minutes, the BOC-piperidine compound of part B (2.6 g, 10 mmol) in THF (10 mL) was added dropwise. After 1.5 hours the solution was cooled to minus 60 degrees Celsius and the disulfide of part A (2.0 g, 10 mmol) in THF (7 mL) was added. The solution was stirred at ambient temperature for 2 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (1.8 g, 40%).

Part D: To a solution of the sulfide of part C (1.8 g, 3.95 mmol) in dichloromethane (75 mL) cooled to zero degrees C, was added m-chloroperbenzoic acid (1.7 g, 7.9 mmol). The solution was stirred for 1.5 hours followed by dilution with H_2O and extraction with dichloromethane. The organic layer was washed with 10 percent Na_2SO_3, H_2O, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (1.15 g, 59%).

Part E: To a solution of the sulfone of part D (800 mg, 1.63 mmol) in THF (9 mL) and ethanol (9 mL) was added NaOH (654 mg, 16.3 mmol) in H_2O (3 mL). The solution was heated at sixty-five degrees Celsius for 18 hours. The solution was concentrated in vacuo and the residue was dissolved in H_2O. Following acidification with 2N HCl to pH 4, the solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and

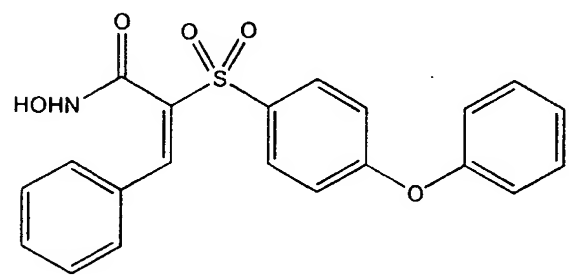
dried over magnesium sulfate. Concentration in vacuo provided the acid as a white foam (790 mg, quantitative yield). analytical calculated for $C_{23}H_{27}NO_7S$: C, 59.86; H, 5.90; N, 3.04; S, 6.95. Found: C, 59.49; H, 6.37; N, 2.81; S, 6.59.

Part F: To a solution of the acid of part G (730 mg, 1.58 mmol) in DMF (9 mL) was added HOBT (256 mg, 1.90 mmol) followed by EDC (424 mg, 2.21 mmol), 4-methylmorpholine (0.521 mL, 4.7 mmol) and 50 percent aqueous hydroxylamine (1.04 mL, 15.8 mmol). The solution was stirred for 20 hours and additional HOBT (256 mg), EDC (424 mg) and 50 percent aqueous hydroxylamine (1.04 mL) were added. After an additional 24 hours of stirring the solution was diluted with H_2O, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Reverse phase HPLC (acetonitrile/H_2O) provided the hydroxamate as a white solid (460 mg, 61%). HPLC purity: >99%. analytical calculated for $C_{23}H_{28}N_2O_7S$: C, 57.97; H, 5.92; N, 5.88; S, 6.73. Found: C, 57.95; H, 6.02; N, 5.81; S, 6.85.

Part G: Into a solution of the hydroxamate of part F (385 mg, 0.808 mmol) in ethyl acetate (25 mL), cooled to zero degrees Celsius, was bubbled HCl gas for 5 minutes. After standing for 30 minutes, the solution was concentrated in vacuo. Trituration with ethyl ether provided the title compound as a white solid (330 mg, quantitative yield). MS(CI) MH^+ calculated for $C_{18}H_{20}N_2O_5S$: 377, found 377. HRMS calculated for $C_{18}H_{20}N_2O_5S$: 377.1171, found 377.1170. analytical calculated for $C_{18}H_{20}N_2O_5S{\bullet}1.1HCl{\bullet}0.25H_2O$: C,

51.35; H, 5.17; N, 6.65; S, 7.62; Cl, 9.26. Found: C, 51.58; H, 5.09; N, 6.55; S, 8.02; Cl, 9.09.

Example 5: Preparation of (E) N-hydroxy-2-[(4-phenoxyphenyl)sulfonyl]-3-phenyl-2-propenamide



Part A: To a solution of 4-(phenoxy)benzenethiol (5.00 g, 24.7 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added t-butylbromoacetate (3.99 mL, 24.7 mmol). Following the addition of triethylamine (3.60 mL, 25.8 mmol) the solution was stirred for 40 minutes The solution was concentrated in vacuo and the resulting residue was dissolved in ethyl acetate and washed with H_2O and saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the sulfide as an oil (7.9 g, quantitative yield).

Part B: To a solution of the sulfide of part A (7.9 g, 24.7 mmol) in methanol (180 mL) and H_2O (20 mL) was added Oxone® (38.4 g, 62.5 mmol) and the mixture was stirred for 22 hours. The mixture was acidified to pH 4 with 2.5N NaOH and decanted to remove insoluble salts. The decantate was

concentrated to one-half volume and partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a yellow solid (5.79 g, 67%).

Part C: To a solution of the sulfone of part B (2.5064 g, 7.20 mmol) and benzaldehyde (0.748 mL, 7.36 mmol) in benzene (20 mL) were added acetic acid (0.15 mL) and piperidine (0.05 mL). The solution was heated to reflux for 2 hours and the condensate was collected via a Dean-Stark trap. After an additional 1.5 hours of reflux, the solution was returned to ambient temperature and stirred for 18 hours. The solution was diluted with ethyl acetate and washed with H_2O and saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) followed by trituration (ethyl ether/hexane) provided the unsaturated sulfone as a white solid (1.97 g, 73%). HPLC purity: >98%.

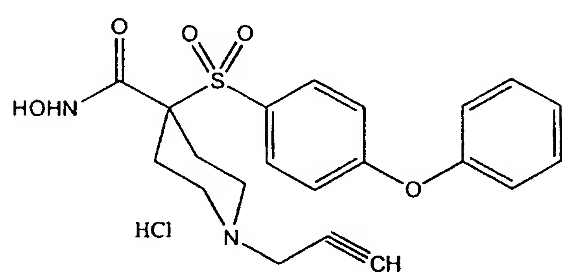
Part D: Into a solution of the unsaturated sulfone of part C (0.5053 g, 1.16 mmol) was bubbled HCl gas for 1 hour. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with H_2O and dried over Na_2SO_4. Concentration in vacuo provided the acid as an oil (0.41 g, 93%).

Part E: To a solution of the acid of part D (461 mg, 1.21 mmol) was added thionyl chloride (3.0 mL) and the solution was heated to one hundred degrees Celsius for 1 hour. Concentration in vacuo

provided the acid chloride as an amber oil (380 mg, 79%).

Part F: To a solution of the acid chloride of part E (380 mg, 0.95 mmol) in THF (20 mL) was added 50 percent aqueous hydroxylamine (1.7 mL, 9.5 mmol). The solution was stirred at zero degrees Celsius for 1 hour. The solution was diluted with ethyl acetate, washed with H_2O and saturated NaCl, and dried over Na_2SO_4. Reverse phase chromatography (on silica, acetonitrile/H_2O) followed by trituration (ethyl ether/hexane) provided the title compound as a white solid (131 mg, 35%). HPLC purity: >97%.

Example 6: Preparation of N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: A solution of 4-(phenoxy)benzenethiol (2.03 g, 10.0 mmol) in DMSO (20 mL) was heated to 65 degrees Celsius for 5 hours. The solution remained at ambient temperature for 18 hours. The solution was extracted with ethyl acetate and the combined organic layers were washed with H_2O and saturated NaCl, and dried over magnesium sulfate.

Concentration in vacuo provided the disulfide as a yellow oil (2.3 g, quantitative yield).

Part B: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2 g, quantitative yield).

Part C: To a solution of diisopropylamine (2.8 mL, 20 mmoL) in THF (30 mL), cooled to minus seventy-eight degrees Celsius, was added n-butyl lithium (12.5 mL, 20 mmol) dropwise. After 15 minutes, the BOC-piperidine compound of part B (2.6 g, 10 mmol) in THF (10 mL) was added dropwise. After 1.5 hours the solution was cooled to minus sixty degrees Celsius and the disulfide of part A (2.0 g, 10 mmol) in THF (7 mL) was added. The solution was stirred at ambient temperature for 2 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (1.8 g, 40%).

Part D: To a solution of the sulfide of part C (1.8 g, 3.95 mmol) in dichloromethane (75 mL) cooled to zero degrees Celsius, was added m-chloroperbenzoic acid (1.7 g, 7.9 mmol). The

solution was stirred for 1.5 hours followed by dilution with H_2O and extraction with dichloromethane. The organic layer was washed with 10 percent Na_2SO_4, H_2O, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (1.15 g, 59%).

Part E: Into a solution of the sulfone of part D (3.56 g, 7.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius was bubbled HCl gas for 5 minutes. Concentration in vacuo followed by trituration with ethyl ether provided the amine hydrochloride salt as a white solid (3.5 g, quantitative yield). MS(CI) MH^+ calculated for $C_{20}H_{23}NO_5S$: 390, found 390.

Part F: To a solution of the amine hydrochloride salt of part E (2.6 g, 6 mmol) and K_2CO_3 (1.66 g, 12 mmol) in DMF (50 mL) was added propargyl bromide (892 mg, 6 mmol) and the solution was stirred at ambient temperature for 4 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine as a white solid (2.15 g, 82%).

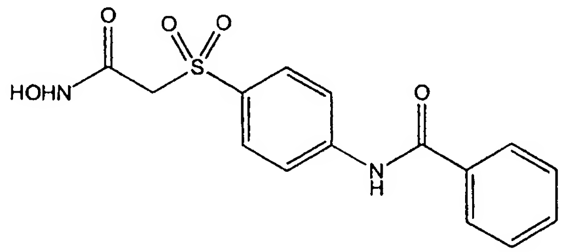
Part G: To a solution of the propargyl amine of part F (2.15 g, 5 mmol) in THF (30 mL) and ethanol (30 mL) was added NaOH (2.0 g, 50 mmol) and the solution was heated at 65 degrees Celsius for 48 hours. The solution was concentrated in vacuo and

the aqueous residue was acidified to a pH value of 5. Vacuum filtration of the resulting precipitate provided the acid as a white solid (2.04 g, quantitative yield).

Part H: To a solution of the acid of part G (559 mg, 1.4 mmol) in dichloromethane (5 mL) was added triethylamine (0.585 mL, 4.2 mmol) and 50 percent aqueous hydroxylamine (0.925 mL, 14.0 mmol) followed by bromotris(pyrrolidino)phosphonium hexafluourphosphate (PyBroP®; 718 mg, 1.54 mmol). The solution was stirred at ambient temperature for 4 hours. The solution was diluted with H_2O and extracted with dichloromethane. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the hydroxamate as a white solid (140 mg, 25%). Analytical calculation for $C_{21}H_{22}N_2O_5S$: C, 60.85; H, 5.37; N, 6.76; S, 7.74. Found: C, 60.47; H, 5.35; N, 6.61; S, 7.46.

Part I: To a solution of the hydroxamate of part H (121 mg, 0.292 mmol) in methanol (2 mL) cooled to zero degrees Celsius was added acetyl chloride (0.228 mL, 0.321 mmol) in methanol (1 mL). After stirring at ambient temperature for 30 minutes the solution was concentrated under a stream of N_2. Trituration with ethyl ether provided the title compound as a white solid (107 mg, 81%). Analytical calculation for $C_{21}H_{22}N_2O_5S \bullet HCl \bullet 0.3H_2O$: C, 55.27; H, 5.21; N, 6.14. Found: C, 54.90; H, 5.37; N, 6.07.

Example 7: Preparation of N-[4-[[2-(hydroxyamino)-2-oxoethyl]sulfonyl]phenyl]benzamide



Part A: To a suspension of 2-(4-aminophenylthio)acetic acid (20.00 g, 0.109 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added thionyl chloride (24.0 mL, 0.327 mmol) dropwise. Additional methanol was added (100 mL) and the suspension was heated to reflux for 2 hours. The solution was concentrated in vacuo and the residue was dissolved into H_2O and neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the methyl ester as a dark purple oil (22.75 g, quantitative yield). HPLC purity: 99%.

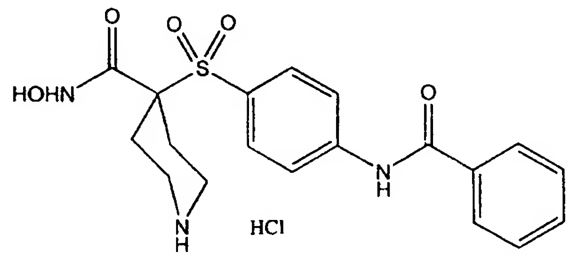
Part B: To a solution of the methyl ester of part A (5.00 g, 25.35 mmol) and triethylamine (7.07 mL, 50.70 mmol) in dichloromethane (50 mL) was added benzoyl chloride (3.24 mL, 27.89 mmol) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate, THF and H_2O. The organic layer was washed with H_2O

and saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the benzamide as a purple solid (7.06 g, 92%). HPLC purity: 98%. MS(CI) $M+Li^+$ calculated for $C_{16}H_{15}NO_3S$: 308, found 308.

Part C: To a solution of the benzamide of part B (4.00 g, 13.27 mmol) in THF (100 mL) and H_2O (10 mL) cooled to zero degrees Celsius was added Oxone® (potassium monopersulfate; 24.47 g, 39.81 mmol). The slurry was stirred overnight (about eighteen hours) at ambient temperature. The mixture was filtered to remove excess Oxone® and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H_2O and saturated NaCl, and then dried over Na_2SO_4. Concentration in vacuo provided the sulfone as a pink solid (4.11 g, 93%). HPLC purity: 98%. MS(CI) $M+Li^+$ calculated for $C_{16}H_{15}NO_5S$: 340, found 340.

Part D: To a solution of the sulfone of part C (400 mg, 1.2 mmol) in THF (9 mL) was added 50 percent aqueous hydroxylamine (5.0 mL). The solution was stirred for 8 hours and was concentrated in vacuo. Trituration with hot ethyl ether provided the title compound as an off-white solid (348 mg, 78%). HPLC purity: 97%. MS(CI) MH^+ calculated for $C_{17}H_{14}N_2O_5S$: 335, found 335.

Example 8: Preparation of N-[4-[[2-(hydroxyamino)-2-oxo-1-(piperidin-4-yl)ethyl]sulfonyl]-phenyl]-benzamide, monohydrochloride



Part A: To a solution of diethanolamine (22.16 g, 0.211 mol) in THF (100 mL) cooled to zero degrees Celsius was added di-t-butyl dicarbonate (46.0 g, 0.211 mol) and the solution was stirred at ambient temperature for 20 hours. The solution was concentrated in vacuo and the resulting residue was filtered through a silica pad (5 percent methanol/95 percent dichloromethane) to provide the diol as a clear oil (45.06 g, quantitative yield). MS(CI) MH^+ calculated for $C_9H_{19}O_4S$: 206, found 206.

Part B: To a suspension of 2-(4-aminophenylthio)acetic acid (20.00 g, 0.109 mmol) in methanol (100 mL) cooled to zero degrees Celsius thionyl chloride (24.0 mL, 0.327 mmol) was added dropwise. After additional methanol was added (100 mL), the suspension was heated to reflux for 2 hours. The composition was concentrated in vacuo, the residue was dissolved in H_2O and neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the methyl ester as a dark purple oil (22.75 g, quantitative yield). HPLC purity: 99%.

Part C: To a solution of the methyl ester of part B (5.00 g, 25.35 mmol) and triethylamine (7.07 mL, 50.70 mmol) in dichloromethane (50 mL) was added benzoyl chloride (3.24 mL, 27.89 mmol) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate, THF and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the benzamide as a purple solid (7.06 g, 92%). HPLC purity: 98%.

Part D: To a solution of the benzamide of part C (4.00 g, 13.27 mmol) in THF (100 mL) and H_2O (10 mL) cooled to zero degrees Celsius was added Oxone® (24.47 g, 39.81 mmol). The slurry was stirred overnight (about eighteen hours) at ambient temperature. The mixture was filtered to remove excess Oxone® and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H_2O and saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the sulfone as a pink solid (4.11 g, 93%). HPLC purity: 98%.

Part E: To a solution of the diol of part A (1.03 g, 5.00 mmol) and the methyl ester of part D (2.00 g, 6.00 mmol) in THF (100 mL) was added the 1,1'-(azodicarbonyl)dipiperidine (5.05 g, 20.00 mmol). To this slurry was added trimethyl phosphine (20.00 mL of a 1.0M solution in THF, 20.00 mmol). The mixture stirred for 1 hour at ambient temperature and then was heated at 40 degrees Celsius for 18 hours. After the slurry returned to ambient

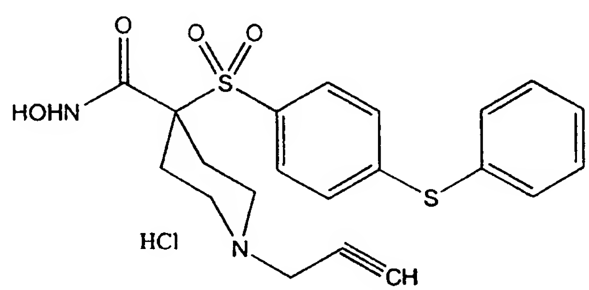
temperature, ethyl ether was added and the insoluble solids were removed by filtration. The filtrate was concentrated in vacuo and the resulting residue was dissolved into ethyl acetate, washed with H_2O and saturated NaCl, and then dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the piperidine compound as a yellow solid (600 mg, 24%). MS(CI) MH^+ calculated for $C_{25}H_{30}N_2O_7S$: 503, found 503.

Part F: To a solution of the piperidine compound of part E (950 mg, 1.89 mmol) in THF (10 mL) was added potassium silanolate (970 mg, 7.56 mmol) and the solution was stirred at ambient temperature for 72 hours. The solution was diluted with H_2O, acidified to pH 2 with 1M HCl, and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provided the acid as a yellow solid (772 mg, 84%).

Part G: To a solution of the acid of part F (772 mg, 1.48 mmol) in DMF (9 mL) was added HOBT (240 mg, 1.77 mmol), 4-methylmorpholine (0.488 mL, 4.44 mmol), O-tetrahydropyranyl hydroxyamine (538 mg, 4.54 mmol) and EDC (397 mg, 2.07 mmol). The solution stirred at ambient temperature for 2 hours. Following concentration in vacuo the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxylamine as a white solid (608 mg, 70%). HPLC purity: >99%).

Part H: To a solution of the protected hydroxylamine of part G (596 g, 1.01 mmol) in dioxane (3 mL) and methanol (1 mL) was added 4M HCl in dioxane (2.50 mL, 10.14 mmol) and the solution stirred for 50 minutes at ambient temperature. Trituration with ethyl ether provided the title compound as a white solid (433 mg, 98%). HPLC purity: 98%. MS(CI) MH^+ calculated for $C_{19}H_{21}N_3O_5S$: 404, found 404.

Example 9: Preparation of N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight (about eighteen hours) at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (ethyl acetate/hexanes) and concentrated

in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2 g, quantitative yield).

Part B: A solution of 4-fluorothiophenol (50.29 g, 390 mmol) in DMSO (500 mL) was heated to 65 degrees Celsius for 6 hours. The reaction was quenched into wet ice and the resulting solid was collected by vacuum filtration to provide the disulfide as a white solid (34.4 g, 68.9%).

Part C: To a solution of the BOC-piperdine compound of part A (16 g, 62 mmol) in THF (300 mL) cooled to minus 50 degrees Celsius was added lithium diisopropylamide (41.33 mL, 74 mmol) and the solution was stirred for 1.5 hours at zero degrees Celsius. To this solution was added the disulfide of part B (15.77 g, 62 mmol), and the resulting solution was stirred at ambient temperature for 20 hours. The reaction was quenched with the addition of H_2O and the solution was concentrated in vacuo. The aqueous residue was extracted with ethyl acetate and the organic layer was washed with 0.5N KOH, H_2O, and saturated NaCl. Chromatography (on silica, hexane/ethyl acetate) provided the sulfide as an oil (18.0 g, 75%).

Part D: To a solution of the sulfide of part C (16.5 g, 43 mmol) in dichloromethane (500 mL) cooled to zero degrees Celsius was added 3-chloroperbenzoic acid (18.0 g, 86 mmol) and the solution was stirred for 20 hours. The solution was diluted with H_2O and extracted with dichloromethane. The organic layer was washed with 10 percent Na_2SO_3, H_2O, and saturated NaCl and dried over magnesium

sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (10.7 g, 60%).

Part E: Into a solution of the sulfone of part D (10 g, 24.0 mmol) in ethyl acetate (250 mL) was bubbled HCl gas for 10 minutes followed by stirring at ambient temperature for 4 hours. Concentration in vacuo provided the amine hydrochloride salt as a white solid (7.27 g, 86%).

Part F: To a solution of the amine hydrochloride salt of part E (5.98 g, 17.0 mmol) in DMF (120 mL) was added potassium carbonate (4.7 g, 34.0 mmol) followed by propargyl bromide (2.02 g, 17.0 mmol) and the solution was stirred for 4 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O, and the organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine as a yellow oil (5.2 g, 86%).

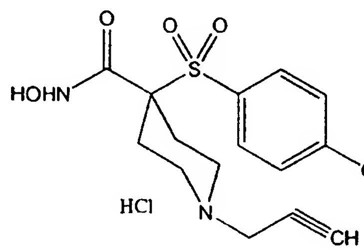
Part G: To a solution of the propargyl amine of part F in DMF (15 mL) was added thiophenol (0.80 mL, 7.78 mmol) and $CsCO_3$ (2.79 g, 8.56 mmol) and the solution was heated to 70 degrees Celsius for 6 hours. The solution was partitioned between ethyl ether and H_2O. The organic layer was washed with H_2O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the S-phenoxyphenyl compound as an oil (1.95 g, 56%).

Part H: To a solution of the S-phenoxyphenyl of part G (1.81 g, 4.06 mmol) in ethanol (21 mL) and H_2O (3.5 mL) was added KOH (1.37 g, 24.5 mmol) and the solution was heated to 105 degrees Celsius for 4.5 hours. The solution was acidified to a pH value of 1 with concentrated HCl solution and then concentrated to provide the acid as a yellow residue that was used without additional purification (1.82 g).

Part I: To a solution of the acid of part H (1.82 g, 4.06 mmol) in acetonitrile (20 mL) was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (723 mg, 6.17 mmol) and triethylamine (0.67 mL, 4.86 mmol). To this stirring solution was added EDC (1.18 g, 6.17 mmol) and the solution was stirred for 18 hours. The solution was partitioned between H_2O and ethyl acetate. The organic layer was washed with H_2O, saturated $NaHCO_3$ and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (1.32 g, 63%).

Part J: To a solution of the protected hydroxamate of part I (9.65 g, 18.7 mmol) in methanol (148 mL) cooled to zero degrees Celsius was added acetyl chloride (4.0 mL, 56.2 mmol), and the solution was stirred for 45 minutes at ambient temperature. Concentration in vacuo followed by trituration with ethyl ether provided the title compound as a white solid (8.10 g, 94%). MS(CI) MH^+ calculated for $C_{21}H_{22}N_2O_4S_2$: 431, found 431.

Example 10: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



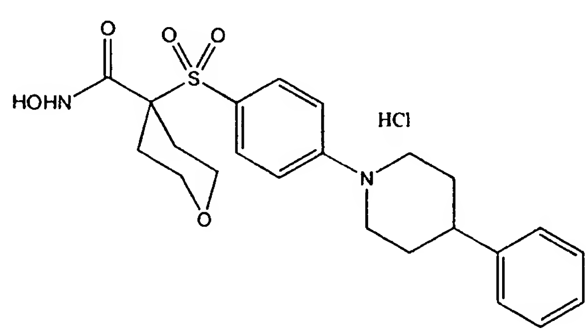
Part A: To a solution of the propargyl amine of Example 9, part F (7.0 g, 19.8 mmol) in DMF (30 mL) were added sesamol (5.52 g, 40 mmol) and potassium carbonate (5.52 g. 40 mmol), and the solution was heated to 85 degrees Celsius for 48 hours. The solution was partitioned between ethyl acetate and H_2O. The organic layer was dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (9.38 g, quantitative yield).

Part B: To a solution of the sulfide of part A (2.72 g, 5.92 mmol) in ethanol (30 mL) and H_2O (5 mL) was added potassium hydroxide (2.0 g, 36 mmol) and the solution was heated to reflux for 4 hours. The solution was acidified to pH=3 with concentrated HCl. The solution was concentrated in vacuo and the residue was dissolved in acetonitrile (30 mL). To this solution was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.05 g, 9.0 mmol), triethylamine (1 mL) and EDC (1.72 g, 9.0 mmol) and the solution was

stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and diluted with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an oil (2.86 g, 93%).

Part C: To a solution of the protected hydroxamate of part B (2.86 g, 5.27 mmol) in methanol (40 mL) was added acetyl chloride (1.13 mL, 15.8 mmol) and the solution was stirred for 3 hours. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H_2O(HCl)) provided the title compound as a white solid (2.2 g, 84%). MS(CI) MH^+ calculated for $C_{22}H_{22}N_2O_7S$: 459, found 459.

Example 11: Preparation of Tetrahydro-N-hydroxy-4-[[4-(4-phenyl-1-piperidinyl)phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a solution of Na (8.97 g, 390 mmol) in methanol (1L) at zero degrees Celsius were added 4-fluorothiophenol (50 g, 390 mmol) and methyl chloroacetate (34.2 mL, 390 mmol), and the solution was stirred for 4 hours at ambient temperature. The solution was filtered to remove salts and the filtrate was concentrated in vacuo to provide the sulfide as a colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide of part A (75.85 g, 380 mmol) in methanol (1L) and H_2O (100 mL) was added Oxone® (720 g, 1.17 mol) and the solution was stirred for 2 hours. The reaction mixture was filtered to remove the excess salts and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H_2O, saturated $NaHCO_3$ and saturated NaCl, and then dried over magnesium sulfate. Concentration in vacuo provide the sulfone as white solid (82.74 g, 94%)

Part C: To a solution of the sulfone of part B (28.5 g, 123 mmol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 270 mmol), bis-(2-bromoethyl)ether (19.3 mL, 147 mmol), 4-dimethylaminopyridine (750 mg, 6 mmol) and tetrabutylammonium bromide (1.98 g, 6 mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was poured into 1N HCl (300 mL) and the resulting precipitate was collected by vacuum filtration. Recrystallization (ethyl acetate/hexane) provided the tetrahydropyran compound as a beige solid (28.74 g, 77%).

Part D: To a solution of the tetrahydropyran compound of part C (1.21 g, 4.0 mmol) in DMSO (10 mL) were added Cs_2CO_3 (3.26 g, 10.0 mmol) and 4-phenylpiperidine (640 mg, 4.0 mmol), and the solution was heated to 90 degrees Celsius for 2 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with 5 percent aqueous $KHSO_4$, saturated $NaHCO_3$ and saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the amine as a white solid (1.2 g, 67%).

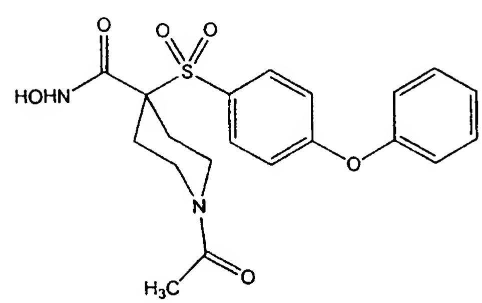
Part E: To a solution of the amine of part D (815 mg, 1.84 mmol) in methanol (5 mL) and THF (5 mL) was added 50 percent aqueous NaOH (2 mL) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was diluted with H_2O and acidified to a pH value of 7. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (680 mg, 86%).

Part F: To a solution of the acid of part E (620 mg, 1.44 mmol) in dichloromethane (10 mL) and DMF (3 mL) were added PyBroP (810 mg, 1.73 mmol), N-methylmorpholine (0.5 mL, 4.3 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (190 mg, 1.59 mmol) and the solution was stirred for 4 hours at ambient temperature. The solution was concentrated in vacuo, the residue dissolved into ethyl acetate and washed with H_2O and saturated NaCl, and then dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as

a white solid (630 mg, 83%). MS(CI) MH^+ calculated for $C_{28}H_{36}N_2O_6S$: 529, found 529.

Part G: To a solution of the protected hydroxamate of part F (600 mg, 1.14 mmol) in dioxane (1.5 mL) and methanol (1.5 mL) was added 4N HCl in dioxane (1.5 mL), and the solution was stirred for 2 hours. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a beige solid (500 mg, 91%). MS(CI) $M+Li^+$ calculated for $C_{23}H_{28}N_2O_5S$: 445, found 445.

Example 12: Preparation of 1-acetyl-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidinecarboxamide



Part A: To a solution of the sulfone of Example 6, part D (2.75 g, 5.6 mmol) in THF (10 mL) and ethanol (10 mL) was added NaOH (2.25 g, 56 mmol), and the solution was heated to 70 degrees Celsius for 18 hours. The solution was concentrated in vacuo, the residue was dissolved into H_2O and extracted with ethyl ether. The aqueous solution was acidified to a pH value of 2 and extracted with ethyl acetate. The

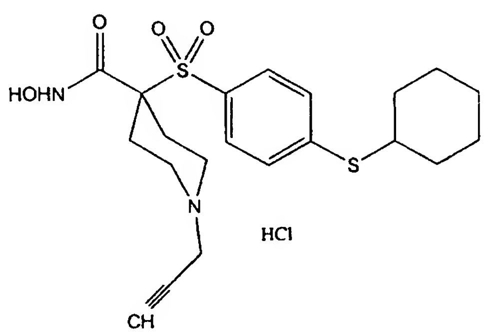
organic layer was dried over magnesium sulfate. Concentration in vacuo provided the crude acid as a solid. A solution of the acid in dichloromethane (6 mL) and trifluoroacetic acid (6 mL) was stirred for 1 hour at ambient temperature. Concentration in vacuo provided the amine hydrochloride salt as a solid (2.3 g, quantitative yield).

Part B: To a solution of the amine hydrochloride salt of part A (2.3 g, < 5.6 mmol) in acetone (10 mL) and H_2O (10 mL) cooled to zero degrees Celsius were added triethylamine (1.17 mL, 8.4 mmol) and acetyl chloride (0.60 mL, 8.4 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo to remove the acetone and the aqueous solution was extracted with ethyl ether. The aqueous layer was acidified to a pH value of 2 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentration in vacuo provided the N-acetyl compound as a white solid (1.5 g, 65.2%).

Part C: To a solution of the N-acetyl compound of part B (0.6 g, 1.49 mmol) in DMF (10 mL) were added EDC (401 mg, 2.1 mmol) followed by 50 percent aqueous hydroxylamine (0.9 mL) and 4-methylmorpholine (0.7 mL, 6.4 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. The organic layer was washed with H_2O and dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the title compound as a

white solid (101 mg, 16%). MS(CI) MH^+ calculated for $C_{20}H_{22}N_2O_6S$: 419, found 419.

Example 13: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



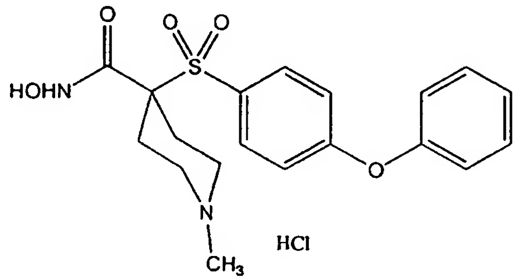
Part A: To a solution of the propargyl amine of Example 9, part F (6.5 g, 18.4 mmol) in DMF (10 mL) were added potassium carbonate (3.81 g, 27.6 mmol) and cyclohexyl mercaptan (3.37 mL, 27.6 mmol). The solution was heated to 100 degrees Celsius for 6.5 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layers were dried over magnesium sulfate. Chromatography (on silica, hexane/ethyl acetate) provided the sulfide as a yellow oil (6.05 g, 73%).

Part B: To a solution of the sulfide of part B (612 mg, 1.4 mmol) in ethanol (8.4 mL) and H_2O (1.4 mL) was added potassium hydroxide (470 mg, 8.4 mmol), and the solution was refluxed for 3 hours.

The solution acidifed to a pH value of 3 and was concentrated in vacuo. The residue was dissolved into acetonitrile (10 mL) and to this solution were added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (230 mg, 2.0 mmol) and triethylamine (0.5 mL) followed by EDC (380 mg, 2.0 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was diluted with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an oil (246 mg, 34%).

Part C: To a solution of the protected hydroxamate of part B (246 mg, 0.47 mmol) in methanol (4 mL) was added acetyl chloride (0.11 mL, 1.5 mmol), and the solution was stirred at ambient temperature for 3 hours. After concentration in vacuo, reverse phase chromatography (on silica, acetonitrile/H_2O(HCl)) provided the title compound as a white solid (223 mg, quantitative yield).

Example 14: Preparation of N-hydroxy-1-methyl-4-[(phenoxyphenyl)sulfonyl]-4-<u>piperidinecarboxamide, monohydrochloride</u>



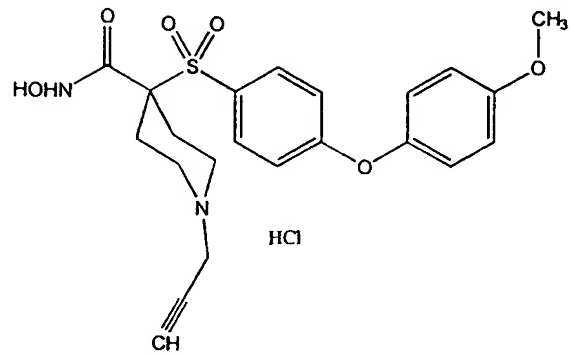
Part A: To a solution of the sulfone of Example 6, part D (2.67 g, 5.5 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL), and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was triturated with ethyl ether to provide the crude amine trifluoroacetic acid salt. To a solution of the crude amine salt in methanol (10 mL) were added formaldehyde (37 percent aqueous solution, 2.0 mL, 27.5 mmol) and borane pyridine (2.2 mL, 22 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate, washed with H_2O and dried over magnesium sulfate. Concentration in vacuo provided the N-methyl compound as a yellow oil (2.17 g, 98%).

Part B: To a solution of the N-methyl compound of part A (2.17 g, 5.4 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (2.0 g, 50 mmol), and the reaction mixture was stirred at minus 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo. The residue was dissolved into H_2O and extracted with ethyl ether. The aqueous

solution was acidified to a pH value of 2 and the resulting solid was collected by vacuum filtration to provide the acid as a white solid (1.8 g, 90%).

Part C: To a solution of the acid of part B (0.5 g, 1.3 mmol) in DMF (10 mL) were added EDC (1.06 g, 5.5 mmol) followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (490 mg, 4.2 mmol) and 4-methylmorpholine (0.76 mL) and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate, washed with H_2O and dried over magnesium sulfate. Concentration in vacuo provided the crude protected hydroxamate. To a solution of the crude hydroxamate in methanol (10 mL) was added acetyl chloride (0.28 mL, 3.9 mmol), and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H_2O(0.0125% HCl) provided the title compound as a white solid (261 mg, 46%). MS(CI) MH^+ calculated for $C_{19}H_{22}N_2O_5S$: 391, found 391.

Example 15: Preparation of N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the propargyl amine of Example 9, part F (2.00 g, 5.66 mmol) in DMF (10 mL) were added cesium carbonate (4.7 g, 14.5 mmol) and 4-methoxythiophenol (1.80 g, 14.5 mmol), and the solution was heated to 95 degrees Celsius for 24 hours. The solution was diluted with ethyl acetate and washed with 1N NaOH and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the phenoxy compound as a solid (2.67 g, quantitative yield).

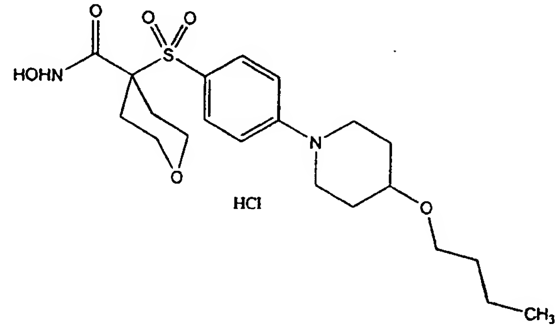
Part B: To a solution of the phenoxy compound of part A (2.40 g, 5.25 mmol) in ethanol (30 mL) and H_2O (6 mL) was added potassium hydroxide (2.0 g, 31.37 mmol), and the solution was heated to reflux for 4 hours. The solution was acidified with concentrated HCl to a pH value of 3 and the residue was collected by vacuum filtration to provide the crude acid that was carried on without additional purification.

Part C: To a solution of the acid of part B (2.25 g, 5.25 mmol) in acetonitrile (30 mL) were added triethylamine (1 mL) and O-tetrahydro-2H-pyran-

2-yl-hydroxylamine (1.34 g, 9.0 mmol). After the solution was stirred for 15 minutes, EDC (1.72 g, 9.0 mmol) was added the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. The ethyl acetate solution was washed with saturated $NaHCO_3$, H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (0.93 g, 33%).

Part D: To a solution of the protected hydroxamate of part C (0.93 g, 1.7 mmol) in methanol (15 mL) was added acetyl chloride (0.36 mL, 5.1 mmol) and the solution was stirred for 3 hours. The solution was concentrated in vacuo to provide the title compound as a white solid (650 mg, 82%). Analytical calculation for $C_{22}H_{24}N_2O_6S$ HCl: C, 54.84; H, 5.24; N, 5.82; S, 6.67; Cl, 6.67. Found: C, 53.10; H, 5.07; N, 5.59; S, 7.04; Cl, 6.32.

Example 16: Preparation of 4-[[4-(4-butoxy-1-piperidinyl)phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a solution of the tetrahydropyran compound of Example 11, part C (1.95 g, 6.46 mmol) in DMSO (25 mL) were added Cs_2CO_3 (7.4 g, 22.6 mmol) and 4-butoxypiperidine (1.25 g, 6.46 mmol) and the solution was heated to 90 degrees Celsius for 1 hour. The solution was quenched with H_2O and extracted with ethyl acetate. The organic layer was washed with 5 percent aqueous $KHSO_4$, saturated $NaHCO_3$ and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/dichloromethane) provided the amine as a yellow oil (1.85 g, 65%).

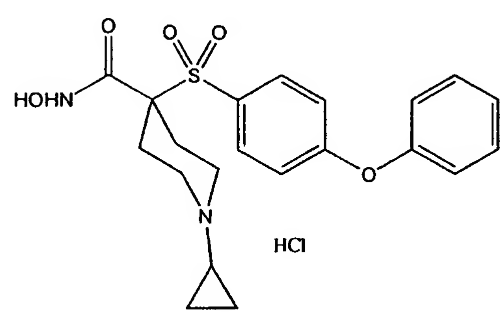
Part B: To a solution of the amine of part A (1.65 g, 3.76 mmol) in THF (10 mL) was added potassium trimethylsilanolate (530 mg, 4.13 mmol), and the solution was stirred for 22 hours at ambient temperature. The solution was concentrated in vacuo and the crude residue was used as is in the next reaction.

Part C: To a solution of the crude acid of part B (1.74 g, 3.76 mmol) in dichloromethane (10 mL) were added PyBroP (2.10 g, 4.51 mmol), N-methylmorpholine (1.24 mL, 11.3 mmol) and O-

tetrahydro-2H-pyran-2-yl-hydroxylamine (484 mg, 4.14 mmol), and the solution was stirred for 30 minutes at ambient temperature. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H_2O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/ hexane/methanol) provided the protected hydroxamate as a colorless oil (1.5 g, 76% over two steps).

Part D: To a solution of the protected hydroxamate of part C (1.25 g, 2.4 mmol) in dioxane (3 mL) was added 4N HCl in dioxane (3 mL), and the solution was stirred for 15 minutes. After methanol (3 mL) was added the solution was stirred for 5 hours at ambient temperature. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (1.0 g, 88%). MS(CI) MH^+ calculated for $C_{21}H_{32}N_2O_6S$: 441, found 441.

Example 17: Preparation of 1-cyclopropyl-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the amine hydrochloride salt of Example 6, part E (2.13 g, 5.0 mmol) in methanol (25 mL) was added 3A molecular sieves, acetic acid (2.86 mL, 50 mmol) and the solution was stirred for 5 minutes. To this solution was added ((1-ethyoxycyclopropyl)oxy)-trimethylsilane (6.08 mL, 30 mmol) followed by sodium cyanoborohydride (1.41 g, 22.0 mmol), and the solution was heated to reflux for 18 hours. The excess salts and sieves were collected by filtration and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 1N NaOH, H_2O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the cyclopropyl amine as a white solid (1.90 g, 86%).

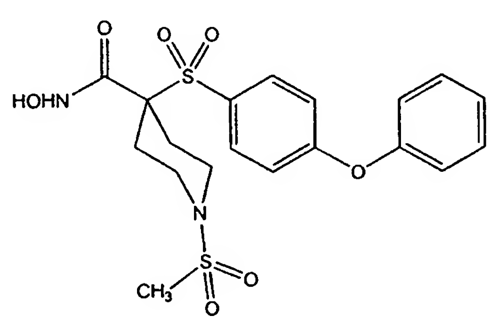
Part B: To a solution of the cyclopropyl amine of part A (1.9 g, 4.2 mmol) in THF (12 mL) and ethanol (12 mL) was added NaOH (1.71 g, 4.3 mmol) in H_2O (10 mL), and the solution was heated to 62 degrees Celsius for 20 hours. The solution was concentrated in vacuo and the residue was diluted with H_2O and acidified to a pH value of 5 with 1N HCl. The resulting solid was collected by vacuum filtration to provide the acid as a white solid (1.49 g, 82%). MS(CI) MH^+ calculated for $C_{21}H_{23}NO_5S$: 402, found 402. HRMS calculated for $C_{21}H_{23}NO_5S$: 402.1375, found 402.1350.

Part C: To a solution of the acid of part C (1.49 g, 3.4 mmol) in dichloromethane (50 mL) was added triethylamine (1.42 mL, 10.21 mmol) followed by

50 percent aqueous hydroxylamine (2.25 mL, 34.0 mmol) and PyBroP (3.17 g, 6.8 mmol), and the solution was stirred for 72 hours. The mixture was diluted with H_2O and the organic layer was separated, washed with saturated NaCl and dried over magnesium sulfate. Concentration in vacuo followed by reverse phase chromatography (on silica, acetonitrile/H_2O) provided the hydroxamate.

The hydrochloride salt was prepared by dissolving the free base (830 mg, 2.0 mmol) in methanol (20 mL) followed by the addition of acetyl chloride (0.17 mL, 2.0 mmol). The solution was stirred for 10 minutes at zero degrees Celsius. The resulting white solid was collect by vacuum filtration and washed with cold ethyl ether to provide the title compound (595 mg, 66%). HRMS calculated for $C_{21}H_{24}N_2O_5S$: 416.1407, found 416.1398. Analytical calculation for $C_{21}H_{24}N_2O_5S$: C, 55.68; H, 5.56; N, 6.18; S, 7.08; Cl, 7.83. Found: C,55.39; H, 5.72; N, 6.15; S, 7.29; Cl, 8.17.

Example 18: Preparation of N-hydroxy-1-(methylsulfonyl)-4-(phenoxyphenyl)-sulfonyl]-4-piperidinecarboxamide



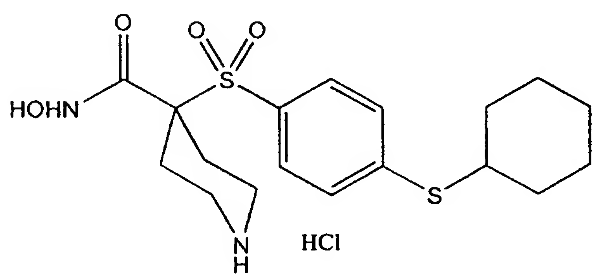
Part A: To a solution of the amine hydrochloride salt of Example 6, part E (1.06 g, 2.5 mmol) in dichloromethane (10 mL) were added triethylamine (0.76 mL, 5.5 mmol) and methanesulfonyl chloride (0.23 mL, 3.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the methanesulfonamide as a solid (2.1 g, 58%).

Part B: To a solution of the methanesulfonamide of part A (2.0 g, 4.15 mmol) in ethanol (12 mL) and H_2O (12 mL) was added NaOH (1.66 g, 41.5 mmol), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and the remaining aqueous solution was acidified to a pH of 4. The solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the acid as a yellow foam (1.46 g, 80%).

Part C: To a solution of the acid of part B (1.46 g, 3.38 mmol) in dichloromethane (50 mL) were added triethylamine (1.41 mL, 10.1 mmol), 50 percent aqueous hydroxylamine (2.2 mL, 33.8 mmol) and PyBroP (3.16 g, 6.76 mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was diluted with H_2O and the organic layer was separated

and washed with saturated NaCl, and then dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H_2O) followed by trituration with ethyl ether provide the title compound as a white solid (160 mg, 11%). Analytical calculation for $C_{19}H_{22}N_2O_7S_2$: C, 50.21; H, 4.88; N, 6.16; S, 14.11. Found: C, 48.72; H, 5.36; N, 5.61; S, 12.81.

Example 19: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



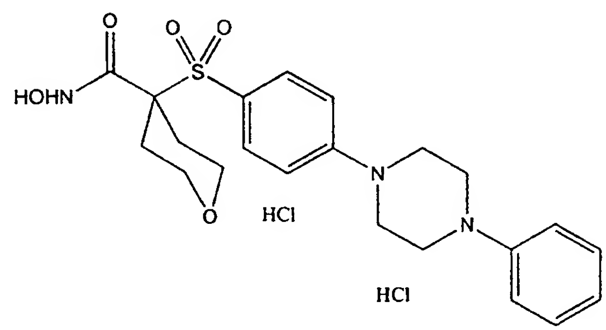
Part A: To a solution of the sulfone of Example 9, part D (10.1 g, 24.0 mmol) in DMF (20 mL) were added K_2CO_3 (5.0 g, 36.0 mmol) and cyclohexylmercaptan (4.4 mL, 36.0 mmol), and the solution was heated at 85 degrees Celsius for 6.5 hours. The solution was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a oil (8.2 g, 67%).

Part B: To a solution of the sulfide (2.32 g, 4.5 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (1.81 g, 45 mmol) in H_2O (10 mL), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 2. The solution was extracted with dichloromethane and dried over magnesium sulfate. Concentration in vacuo provided the acid as a white solid (830 mg, 38%).

Part C: To a solution of the acid of part B (2.0 g, 4.0 mmol) in dichloromethane (25 mL) were added N-methylmorpholine (1.32 mL, 12.0 mmol), PyBroP (2.12 g, 2.12 mmol) and 50 percent aqueous hydroxylamine (2.6 mL, 40 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was diluted with H_2O and the layers were separated. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/methanol) provided the hydroxamate as a white solid (1.4 g, 70%).

Part D: Into a solution of the hydroxamate of part C (1.31 g, 2.63 mmol) in ethyl acetate (70 mL) cooled to zero degrees Celsius was bubbled HCl gas for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H_2O(HCl)) provided the title compound as a white solid (378 mg, 33%). Analytical calculation for $C_{18}H_{26}N_2O_4S_2$: C, 49.70; H, 6.26; N, 6.44; S, 14.74; Cl, 8.15. Found: C, 48.99; H, 6.34; N, 6.24; S,14.66; Cl, 8.56.

Example 20: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-phenyl-1-piperazinyl)phenyl]sulfonyl]-2H-pyran-4-carboxamide, dihydrochloride



Part A: To a solution of the tetrahydropyran compound of Example 11, part C (1.96 g, 6.5 mmol) in DMSO (20 mL) were added Cs_2CO_3 (4.9 g, 15 mmol) and 4-phenylpiperazine (1.1 mL, 7.15 mmol), and the solution was heated to 90 degrees Celsius for 45 minutes. The solution was quenched by the addition of H_2O and was extracted with ethyl acetate. The organic layer was washed with 5 percent aqueous $KHSO_4$, saturated $NaHCO_3$ and saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the amine as a beige solid (1.7 g, 59%).

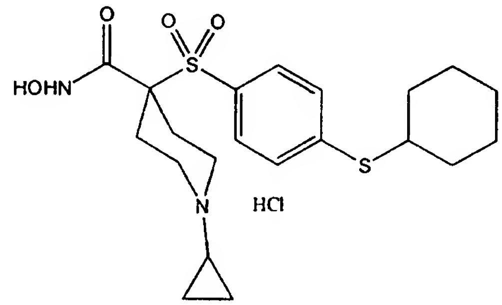
Part B: To a solution of the amine of part A (1.5 g, 3.38 mmol) in THF (20 mL) was added potassium trimethylsilanolate (480 mg, 3.72 mmol), and the solution was stirred at ambient temperature for 22 hours. Concentration in vacuo provided the

crude acid salt to be used without purification in the next step.

Part C: To a solution of the acid salt of part B (1.58 g, 3.38 mmol) in dichloromethane (10 mL) and DMF (3 mL) were added PyBroP (1.89 g, 4.06 mmol), N-methylmorpholine (1.1 mL, 10.1 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (435 mg, 3.72 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H_2O and the organic layer was washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, dichloromethane/methanol) provided the protected hydroxamate as a white foam (1.7 g, 95% over two steps).

Part D: To a solution of the protected hydroxamate of part C (1.28 g, 2.4 mmol) in dioxane (5 mL) and methanol (5 mL) was added 4N HCl in dioxane (5 mL), and the solution was stirred for 2 hours at ambient temperature. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (900 mg, 73%). MS(CI) MH^+ calculated for $C_{22}H_{27}N_3O_5S$: 446, found 446.

Example 21: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-1-cyclopropyl)-N-hydroxy-4-piperidine carboxamide, monohydrochloride



Part A: To a solution of the sulfone of Example 9, part D (10.1 g, 24.0 mmol) in DMF (20 mL) were added K_2CO_3 (5.0 g, 36.0 mmol) and cyclohexylmercaptan (4.4 mL, 36.0 mmol), and the solution was heated at 85 degrees Celsius for 6.5 hours. The solution was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a oil (8.2 g, 67%).

Part B: HCl gas was bubbled for 30 minutes into a solution of the sulfide of part B (8.2 g, 17.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius. The solution was concentrated in vacuo to provide the amine as a white solid (5.99 g, 79%). MS(CI) MH^+ calculated for $C_{20}H_{29}NO_4S$: 412, found 412.

Part C: To a solution of the amine of part B (2.24 g, 5.0 mmol) in methanol (20 mL) was added acetic acid (2.86 mL, 50 mmol) followed by (1-ethoxycyclopropyl) oxytrimethylsilane (6.03 mL, 30 mmol) and sodium borohydride (1.41 g, 22.5 mmol), and the solution was refluxed for 18 hours. The solution

was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with 1N NaOH, H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the cyclopropyl amine as a white solid (1.97 g, 87%).

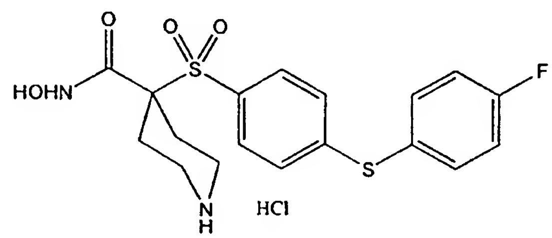
Part D: To a solution of the cyclopropyl amine of part C (1.9 g, 4.2 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (1.68 g, 42.0 mmol) in H_2O (10 mL) and the solution was heated at sixty-eight degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 2. The resulting solid was collected and washed with ethyl ether to provide the acid as a white solid (1.61 g, 81%). HRMS calculated for $C_{21}H_{29}NO_4S_2$: 424.1616, found 424.1615.

Part E: To a solution of the acid of part D (1.61 g, 3.0 mmol) in dichloromethane (30 mL) were added N-methylmorpholine (1.0 g, 9.0 mmol), PyBroP (1.54 g, 3.3 mmol) and 50 percent aqueous hydroxylamine (2.0 mL, 30 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo. The residue was partitioned between ethyl acetate and H_2O, the organic layer washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Filtration through a silica pad (ethyl acetate/methanol) gave the hydroxamate as a white solid (1.07 g, 80%).

Part F: To a solution of the hydroxamate of part F (1.07 g, 2.4 mmol) in cold methanol (2 mL) was added acetyl chloride (0.27 mL, 3.6 mmol), and

the solution was stirred for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (acetonitrile/H_2O(HCl)) provided the title compound as a white solid (245 mg, 21%).

Example 22: Preparation of 4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the sulfone of Example 9, part D (6.0 g, 14.4 mmol) in DMF (30 mL) were added potassium carbonate (2.39 mg, 17.3 mmol) and 4-fluorothiophenol (3.0 mL, 28.1 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was diluted with ethyl acetate and washed with 1N NaOH and saturated NaCl, and thrn dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a solid (6.6 g, 87%).

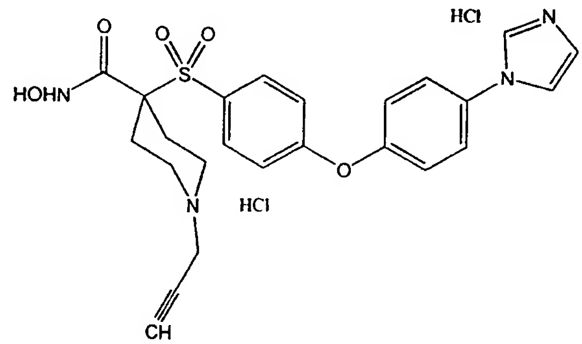
Part B: To a solution of the sulfide of part A (6.6 g, 12.6 mmol) in ethanol (90 mL) and H_2O (20 mL) was added sodium hydroxide (5.04 g, 126 mmol), and the solution was heated at 70 degrees Celsius for 18 hours. The mixture was acidified to a

pH value of 4 and the solution was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/ethanol) provided the solid acid (4.8 g, 79%).

Part C: To a solution of the acid of part B (4.8 g, 10.0 mmol) in DMF (30 mL) was added 4-methylmorpholine (3.03 g, 30.0 mmol) followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (7.45 g, 50.0 mmol) and PyBroP (5.59 g, 12.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (4.0 g, 67%).

Part D: HCl gas was bubbled for 5 minutes into a solution of the protected hydroxamate of part D (4.0 g, 6.7 mmol) in ethyl acetate (120 mL) followed by stirring at ambient temperature for 1.5 hours. The resulting solid was collected by vacuum filtration to provide the title compound as a white solid (1.90 g, 64%). MS(CI) MH^+ calculated for $C_{18}H_{19}N_2O_4S_2F$: 411, found 411.

Example 23: Preparation of N-hydroxy-4-[[4-[4-(1H-imidazol-1-yl)phenoxy] phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, dihydrochloride



Part A: To a solution of the amine hydrochloride salt of Example 9, part F (3.00 g, 8.49 mmol) in DMF (13 mL) were added K_2CO_3 (2.35 g, 17.0 mmol) and 4-(imidazol-1-yl)phenol (2.72 g, 17.0 mmol), and the solution was heated to 85 degrees Celsius for 64 hours. The solution was concentrated and the residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, chloroform/methanol) provided the ethyl ester as a white foam (2.36 g, 56%).

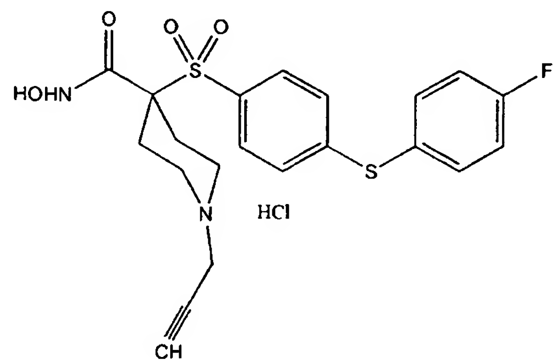
Part B: To a solution of the ethyl ester of part A (2.36 g, 5.33 mmol) in ethanol (2.8 mL) and H_2O (4.6 mL) was added KOH (1.80 g, 32.1 mmol), and the solution was heated to 100 degrees Celsius for 4.5 hours. The solution was acidified to a pH value of 1 with concentrated HCl solution and then concentrated to provide the acid as a tan solid that was used without additional purification (2.87 g).

Part C: To a solution of the acid of part B (2.87 g, 5.33 mmol) in acetonitrile (24 mL) were added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (870

mg, 7.45 mmol), EDC (1.43 g, 7.45 mmol) and N-methylmorpholine (1.21 mL, 11.0 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated and the residue was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (chloroform, methanol) provided the protected hydroxylamine as a white solid (1.62 g, 53%).

Part D: To a solution of the protected hydroxylamine of part C (1.60 g, 2.83 mmol) in methanol (23 mL) was added acetyl chloride (0.61 mL, 8.52 mmol), and the solution was stirred for 1 hour. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the title compound as a white solid (975 mg, 62%). MS(CI) MH^+ calculated for $C_{24}H_{25}N_4O_5S$: 481, found 481. Analytical calculation for $C_{24}H_{25}N_4O_5S$ 2HCl: C, 52.08; H, 4.73; N, 10.12; S, 5.79; Cl, 12.81. Found: C, 51.59; H, 4.84; N, 10.93; S, 5.51; Cl, 11.98.

Example 24: Preparation of 4-[[4-[(4-fluorophenyl)thiophenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the propargyl amine of Example 9, part F (4.06 g, 11.49 mmol) in DMF (20 mL) were added potassium carbonate (3.18 g, 22.98 mmol) and 4-fluorothiophenol (2.95 g, 22.98 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was diluted with ethyl acetate, washed with 1N NaOH and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a solid (4.46 g, 84%).

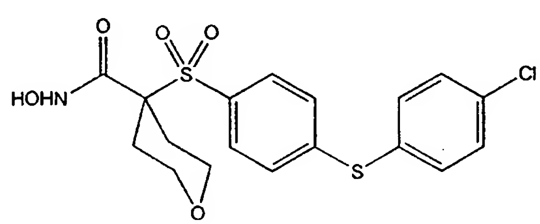
Part B: To a solution of the sulfide of part A (4.46 g, 9.7 mmol) in tetrahydropyran (90 mL), H_2O (30 mL) and ethanol (30 mL) was added NaOH (3.86 g, 97.0 mmol), and the solution was heated to 65 degrees Celsius for 2 hours. The solution was concentrated in vacuo and the residue was dissolved into H_2O and acidified to a pH value of 4 with 2N HCl. The resulting residue was collected by vacuum filtration to provide the acid as a white solid (4.0 g, 95%).

Part C: To a solution of the acid of part B (4.0 g, 9.2 mmol) in DMF (50 mL) and 4-methylmorpholine (2.8 g, 27.7 mmol) was added O-

tetrahydro-2H-pyran-2-yl-hydroxylamine (6.88 g, 46.1 mmol) and PyBroP (5.16 g, 11.1 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. The solution was washed with H_2O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (2.8 g, 56%).

Part D: HCl gas was bubbled for 10 minutes into a solution of the protected amine of part C (2.8 g, 5.1 mmol) in ethyl acetate (100 mL), and the solution was then stirred for 1 hour. The solution was concentrated in vacuo and the solid recrystallized (ethanol) to provide the title compound as a white solid (1.12 g, 45%). MS(CI) MH^+ calculated for $C_{21}H_{21}N_2O_4S_2F$: 449, found 449.

Example 25: Preparation of 4-[[4-[(4-chlorophenyl)-thio]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the tetrahydropyran compound of Example 11, part C (8.0 g, 26.5 mmol) in THF (250 mL) was added potassium

trimethylsilonate (10.2 g, 79.5 mmol), and the solution was stirred for 1.5 hours. The reaction was quenched by the addition of H_2O, acidified to a pH value of 2.5, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Concentration in vacuo provide the acid salt as a white solid (5.78 g, 76%).

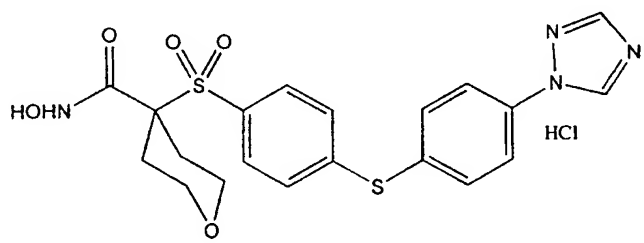
Part B: To a solution of the acid salt of part A (5.4 g, 18.7 mmol) in DMF (35 mL) were added HOBT(3.04 g, 22.5 mmol), N-methylmorpholine (6.2 mL, 56.2 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (6.8 g, 58.1 mmol) and EDC (5.0 g, 26.2 mmol), and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated in vacuo, the residue partitioned between ethyl acetate and H_2O, and the organic layer was washed with 5 percent aqueous $KHSO_4$, H_2O, saturated $NaHCO_3$ and saturated NaCl, and then dried over Na_2SO_4. Concentration in vacuo provided the protected hydroxamate as a white solid (6.34 g, 87%).

Part C: To a solution of p-chlorothiophenol (2.71 g, 18.7 mmol) in DMF (10 mL) was added K_2CO_3 (2.6 g, 18.7 mmol) followed by the protected hydroxamate of part B (2.9 g, 7.5 mmol) and the solution was heated at 75 degrees Celsius for 5 hours. The solution was concentrated in vacuo, the residue partitioned between ethyl acetate and H_2O, the organic layer was washed with saturated NaCl, and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane/methanol) provided the sulfide as a

white foam (3.56 g, 93%). MS(CI) MH^+ calculated for $C_{23}H_{26}ClNO_6S_2$: 512, found 512.

Part D: To a solution of the sulfide of part C (3.5 g, 6.8 mmol) in dioxane (10 mL) was added 4N HCl in dioxane (10 mL). After 10 minutes of stirring, methanol (10 mL) was added with continued stirring for one hour. The solution was concentrated in vacuo. Recrystallization (acetone/hexane) provided the title compound as a white solid (2.4 g, 83%). MS(CI) MH^+ calculated for $C_{18}H_{18}ClNO_5S$: 428, found 428.

Example 26: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-(1H-1,2,4-triazol-1-yl) phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-, carboxamide, monohydrohloride

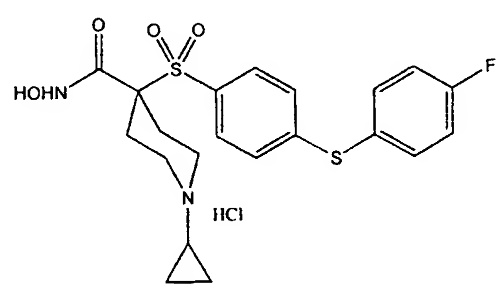


Part A: To a solution of the protected hydroxamate of Example 25, part B (2.9 g, 7.5 mmol) in DMF (10 mL) was added 4-(1,2,4-triazol-1-yl)phenol (2.47 g, 15 mmol) in DMF (5 mL) followed by Cs_2CO_3 (7.33 g, 22.5 mmol), and the solution was heated at 95 degrees Celsius for 5 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H_2O. The organic layer was

washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane/methanol) provided the phenol as a white solid (3.16 g, 80%).

Part B: To a solution of the phenol of part A (2.8 g, 5.3 mmol) in dioxane (10 mL) was added 4N HCl in dioxane (10 mL). After 5 minutes of stirring, methanol (10 mL) was added and stirring was continued for 1 hour. The solution was then poured into ethyl ether, and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (2.44 g, 96%). MS(CI) MH^+ calculated for $C_{20}H_{20}N_4O_6S$: 445, found 445.

Example 27: Preparation of 1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio] phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: HCl gas was bubbled for 7 minutes into a solution of the sulfide of Example 9, part D (7.06 g, 13.5 mmol) in ethyl acetate (150 mL), and the solution was stirred for 15 minutes at zero degrees Celsius. The solution was concentrated in

vacuo to provide the amine as a white solid (6.43 g, quantitative yield).

Part B: To a solution of the amine of part A (6.4 g, 13.9 mmol) in methanol (65 mL) was added acetic acid (7.96 mL, 139 mmol) and a scoop of 3A molecular sieves. To this mixture was added (1-ethoxycyclopropyl)-oxytrimethylsilane (16.8 mL, 84 mmol) followed by sodium cyanoborohydride (3.9 g, 62 mmol). The solution was heated to reflux for 6 hours. The solution was filtered and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate, washed with H_2O, 2N NaOH and saturated NaCl, and dried over magnesium sulfate. Filtration through a pad of silica (hexane/ethyl acetate) provided the cyclopropyl amine as a white solid (6.49 g, quantitative yield).

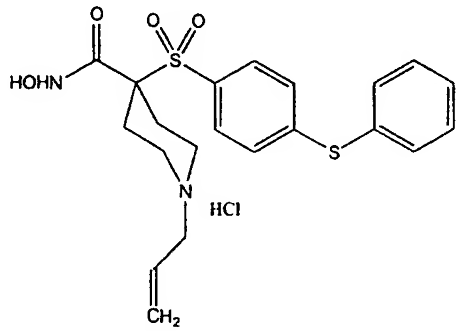
Part C: To a solution of the cyclopropyl amine of part B (6.4 g, 13.8 mmol) in ethanol (30 mL) and THF (30 mL) was added NaOH (5.5 g, 138 mmol) in H_2O (23 mL), and the solution was heated to 65 degrees Celsius for 12 hours. The solution was concentrated in vacuo and the aqueous layer was acidified to a pH value of 2 with 2N HCl. The resulting white precipitate was collected by filtration to provide the acid as a white solid (5.2 g, 87%). MS(CI) MH^+ calculated for $C_{21}H_{22}NO_4S_2F$: 436, found 436.

Part D: To a solution of the acid of part C (2.27 g, 5.2 mmol) in DMF (60 mL) was added HOBT (845 mg, 6.2 mmol) followed by N-methylmorpholine (1.71 mL, 15.6 mmol), EDC (1.40 g, 7.28 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (913 mg, 7.8

mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was concentrated in vacuo, the residue was dissolved into dichloromethane and washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, hexane/ethyl acetate) provided the protected hydroxamate as a white solid (1.95 g, 70%).

Part E: To a solution of the protected hydroxamate of part D (3.2 g, 6.0 mmol) in cold methanol (100 mL) was added acetyl chloride (1.3 mL, 18.0 mmol) in methanol (30 mL), and the solution was stirred at ambient temperature for 4 hours. The solution was concentrated in vacuo and the residue was triturated with ethyl ether to provide the title compound as a white solid (2.86 g, 98%). MS(CI) MH^+ calculated for $C_{21}H_{23}N_2O_4S_2F$: 451, found 451. Analytical calculation for $C_{21}H_{23}N_2O_4S_2F$ $0.25H_2O$ HCl: C, 51.32; H, 5.02; N, 5.70; S, 13.05; Cl, 7.21. Found: C, 50.99; H, 4.91; N, 5.65; S, 13.16; Cl, 7.83.

Example 28: Preparation of N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propenyl)-4-piperidine carboxamide, monohydrochloride



Part A: To a solution of the amine hydrochloride salt of Example 9, part E (4.78 g, 10.8 mmol) in DMF (25 mL) were added K_2CO_3 (2.98 g, 21.6 mmol) and allyl bromide (0.935 mL, 10.8 mmol), and the solution was stirred for 5 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O, and the organic layer was washed with H_2O and saturated NaCl, and dried over magnesium sulfate. Filtration through a pad of silica (hexane/ethyl acetate) provided the allyl amine as an oil (4.80 g, quantitative yield).

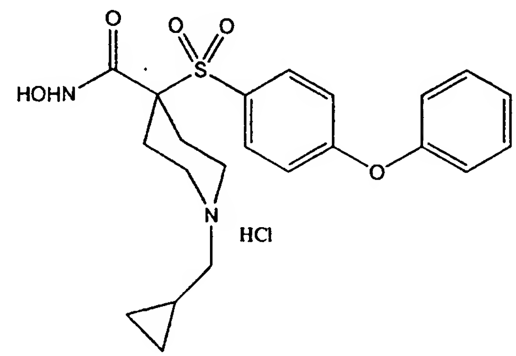
Part B: To a solution of the allyl amine of part A (4.8 g, 10.8 mmol) in ethanol (25 mL) and THF (25 mL) was added NaOH (4.3 g, 108 mmol) in H_2O (20 mL), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and diluted with H_2O. The aqueous solution was acidified to a pH value of 3. The resulting precipitate was collected by vacuum filtration to provide the acid as a beige solid (4.1 g, 84%). MS(CI) MH^+ calculated for $C_{21}H_{23}NO_4S_2$: 418, found 418.

Part C: To a solution of the acid of part B (4.1 g, 9.0 mmol) in DMF (90 mL) was added

HOBT(1.46 g, 11.0 mmol) followed by N-methylmorpholine (2.97 mL, 2.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.58 g, 13.5 mmol) and EDC (2.42 g, 13.0 mmol), and the solution was stirred for 72 hours. The solution was concentrated in vacuo. The residue was dissolved in dichloromethane and washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/methanol) provided the protected hydroxylamine as a white solid (4.11 g, 88%).

Part D: To a solution of the protected hydroxylamine of part C (4.11 g, 8.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius was added acetyl chloride (1.71 mL, 24.0 mmol), and the solution was stirred for 4 hours at ambient temperature. The solution was concentrated in vacuo and trituration with ethyl ether provided the title compound as a white solid (3.53 g, 95%). Analytical calculation for $C_{21}H_{24}N_2O_4S_2$ HCl $0.5H_2O$: C, 52.76; H, 5.48; N, 5.86; S, 13.42; Cl, 7.42. Found: C, 52.57; H, 5.69; N, 6.29; S, 12.59; Cl, 7.80.

Example 29: Preparation of 1-(cyclopropylmethyl)-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidine carboxamide,monohydrochloride



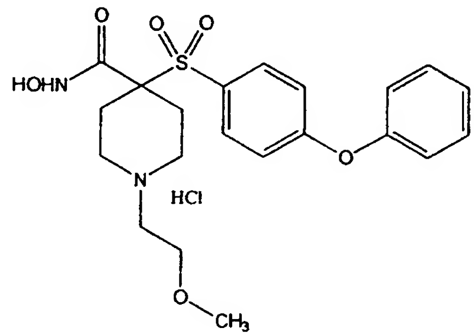
Part A: To a solution of the amine hydrochloride salt of Example 6, part E (2.13 g, 5.0 mmol) in DMF (10 mL) were added K_2CO_3 (1.4 g, 10.0 mmol) and bromomethylcyclopropane (0.48 mL, 5.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O, the organic layer was washed with H_2O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the solid cyclopropylmethylamine (2.09 g, 91%).

Part B: To a solution of the cyclopropylmethylamine of part A (2.0 g, 4.4 mmol) in ethanol (12 mL) and THF (12 mL) was added NaOH (1.75 g, 44 mmol) in H_2O (10 mL), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 5. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (1.58 g, 79%). HRMS calculated for $C_{22}H_{25}NO_5S$: 414.1375, found 414.1334.

Part C: To a solution of the acid of part B (1.58 g, 3.5 mmol) in dichloromethane (50 mL) was added triethylamine (1.46 mL, 10.5 mmol) followed by 50 percent aqueous hydroxylamine (2.3 mL, 35 mmol) and PyBroP (3.26 g, 6.99 mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was washed with H_2O and saturated NaCl, and dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the hydroxamate as a white solid (3.2 g, quantitative yield).

Part D: To a solution of the hydroxamate of part C (1.5 g, 3.5 mmol) in cold methanol (20 mL) was added acetyl chloride (0.25 mL, 3.5 mmol) in methanol (5 mL) and the solution was stirred at zero degrees Celsius for 15 minutes. After the solution had stirred for an additional 30 minutes at ambient temperature, it was concentrated in vacuo. Trituration with ethyl ether provided the title compound as a white solid (229 mg, 7 %).

Example 30: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[(4-phenoxyphenyl)-sulfonyl]-4-piperidine carboxamide, monohydrchloride



Part A: To a solution of the amine HCl salt of part E, Example 6 (2.5 g, 5.87 mmol) and K_2CO_3 (1.6 g, 11.57 mmol) in N,N-dimethylformamide (25 mL) was added 2-bromoethyl methyl ether (0.66 mL, 7.0 mmol) and then stirred at ambient temperature for 18 hours. Then N,N-dimethylformamide was evaporated under high vacuum and residue was diluted with ethyl acetate. The organic layer was washed with water and dried over Mg_2SO_4. Concentration in vacuo provided the methoxyl ethyl amine as light yellow gel (2.63 g, quantitative yield).

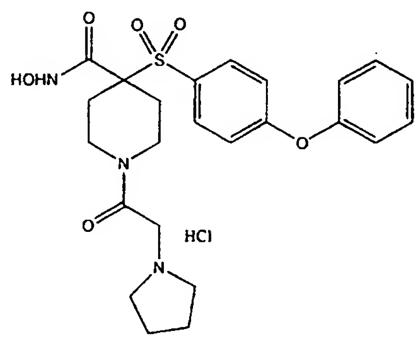
Part B: To a solution of the methoxyl ethyl amine of part A (2.63 g, 5.87 mmol) in tetrahydrofuran (18 mL) and ethanol (18 mL) was added NaOH (2.1 g, 5.25 mmol) in water (6 mL). The solution was heated to reflux for 12 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether (2X100 mL) and was acidified to pH=2. Vacuum filtration of the resulting precipitation provided the acid as a white solid (2.4 g, quantitative yield).

Part C: To a solution of the acid of part B (2.0 g, 4.33 mmol), also containing N-methyl

morpholine (1.8 mL, 16.4 mmol), and O-tetrahydro-2H-pyran-yl-hydroxylamine (0.767 g, 6.44 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.1 g, 16.2 mmol), and solution was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with H_2O and dried over Mg_2SO_4. Concentration in vacuo provided the amide as off white foam (1.60 g, 71.1%).

Part D: To a solution of the amide of part C (1.58 g, 3.05 mmol) in methanol (20 mL) cooled to zero degrees Celsius was added acetyl chloride (0.65 mL, 9.15 mmol) and the resulting solution was stirred at the same temperature for 3 hours. The solution was concentrated and reverse phase chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (0.65 g, 45.5%). Analytical calculation for $C_{21}H_{26}N_2O_6S.HCl.0.75H_2O$: C, 52.06; H, 5.93; N, 5.78; S, 6.62. Found: C, 51.94; H, 5.67; N, 5.91; S, 6.66. HSMS calculated for $C_{21}H_{26}N_2O_6S$: 435.1590, found 435.1571.

Example 31: Preparation of N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-1-(1-pyrrolidinylacetyl)-4-piperidine carboxamide, monohydrochloride



Part A: To a solution of the sulfone of part D, Example 6 (2.75g, 5.6mmol) in tetrahydrofuran (10mL) and ethanol (10mL) was added NaOH (2.25g, 56mmol) in H_2O (20 mL), and the solution was heated to 70 degrees Celsius for 20 hours. The solution was concentrated in vacuo and the dry residue was dissolved in H_2O. The aqueous layer was extracted with ether and was acidified to pH=2 followed by the extraction with ethyl acetate. The combined organic layers were washed again with H_2O and dried over Mg_2SO_4. Concentration in vacuo provided the BOC-acid as white foam (2.3g, 88.8%)

Part B: To a solution of BOC-acid of part A (2.3g, 4.98mmol) in dichloromethane (6 mL) was added trifluroacetic acid (6 mL, 77.8 mmol), and the resulting solution was stirred at ambient temperature for 1 hour. Concentration in vacuo provided the amine as white foam (2.44g, quantitative yield).

Part C: To the solution of the amine of part B (2.4 g, 4.9 mmol) and triethylamine (3.5 mL, 24.4 mmol) in acetone (15 mL) and H_2O (15 mL) was added chloroacetyl chloride (1.2 mL, 14.7 mmol), and solution was stirred at ambient temperature for 20

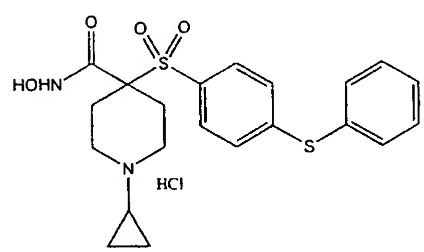
hours. Then acetone was evaporated and aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water and dried over Mg_2SO_4. Concentration in vacuo provided the chloroacetyl amide as light yellow gel (2.78 g, quantitative yield).

Part D: To the solution of the chloroacetyl amide of part C (2.78 g, 4.93mmol) and K_2CO_3 (5 g, 36 mmol) in N,N-dimethylformamide (20 mL) was added pyrolidine (3 mL, 36 mmol). The solution was then stirred at ambient temperature for 18 hours. Then N,N-dimethylformamide was evaporated under high vacuum and reverse phase chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided pyrolidine acetyl amide (0.25g, 10.7%).

Part E: To a solution of the pyrolidine acetyl amide of part D (0.25 g, 0.53 mmol), also containing N-methyl morpholine (0.14 mL, 1.27 mmol), 1-hydroxybenzotriazole (0.17 g, 1.2 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (0.15 g, 1.26 mmol) in N,N-dimethylformamide (4 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.23 g, 1.2 mmol). The solution was then stirred at ambient temperature for 18 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration in vacuo provided the THP amide as white foam (0.25 g, 83.3%).

Part F: To a solution of the amide of part E (0.25 g, 0.437 mmol) in methanol (4 mL) cooled to zero degrees Celsius was added acetyl chloride (0.075 mL, 1.05 mmol), and the resulting solution was stirred at ambient temperature for 2.5 hours. The solution was concentrated and reverse phase chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (80 mg, 29%). Analytical calculation for $C_{24}H_{29}N_3O_6S.HCl.0.9H_2O$: C, 53.36; H, 5.98; N, 7.78. Found: C, 53.61; H, 5.71; N, 7.94. HSMS calculated for $C_{24}H_{29}N_3O_6S$: 488.1855, found 488.1835.

Example 32: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidine carboxamide, monohydrochloride



Part A: A solution of 4-flurothiophenol (50.29 g, 0.39 mmol) in dimethylsulfoxide (500 mL) was heated to 65 degrees Celsius for 5 hours. The solution was cooled to ambient temperature and poured into vigorously stirred ice water. The precipitate was filtered and washed twice with water. Drying

under high vacuum provided the disulfide as a yellow oil (34.39 g, 68.9%) at ambient temperature.

Part B: A solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in tetrahydrofuran (5 mL) was added dropwise over 20 minutes to a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL). The resulting solution was stirred overnight (about eighteen hours) at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (ehyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2g, quantitative yield).

Part C: To a solution of BOC-piperidine compound of part B (15.96 g, 62 mmol) in tetrahydrofuran (300 mL), cooled to minus forty degrees Celsius, was added lithium diisopropylamide (41.33 mL, 74 mmol). The solution was then stirred at minus forty degrees C for one hour and zero degreec C for one-half hour. Then the solution was cooled to minus forty degrees Celsius again and the disulfide of part A (15.77 g, 62 mmol) in tetrahydrofuran (20 mL) was added. The resulting solution as stirred at ambient temperature for 18 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (18 g, 75%).

Part D: To a solution of the sulfide of part C (16.5 g, 43 mmol) in dichloromethane (500 mL) cooled to zero degrees Celsius, was added m-chloroperbenzoic acid (18.5 g, 107 mmol). After 2 hours, the solution was diluted with dichloromethane and washed with 1N KOH, H_2O and dried over $MgSO_4$. Concentration in vacuo provided the sulfone as a solid (21 g, quantitative yield).

Part E: To a solution of sulfone (40 g, 96 mmol) of part D and powdered K_2CO_3 (26 g, 188 mmol) in N,N-dimethylformamide (200 mL) cooled to zero degrees Celsius was added thiolphenol (19.8 mL, 192 mmol), and the reculting composition was then stirred at ambient temperature for 36 hours. That solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with H_2O and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided phenyl thiophenyl Boc-sulfone as white solid (44.34 g, 91%).

Part F: To a solution of phenyl thiophenyl Boc-sulfone of part E (8.6 g, 17 mmol) in dichloromethane (30 mL) cooled to zero degrees Celsius was added trifluroacetic acid (TFA; 30 mL), and the resulting solution was stirred at ambient temperature for 2 hours. Concentration in vacuo provided the amine TFA salt as a light yellow gel (8.7 g, quantitative yield).

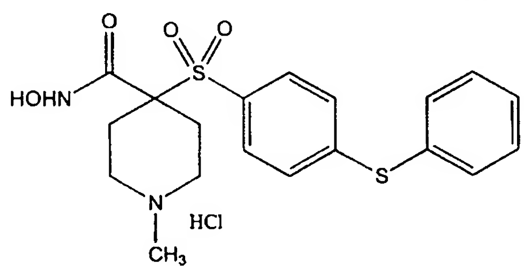
Part G: To a solution of amine TFA salt of part F (6g, 11.9mmol) was added acetic acid (6.8 mL, 119mmol). After 5 minutes stirring at ambient

temperature, (1-ethoxylcyclopropyl)oxytriomethylsilane (14.3 mL, 71.4 mmol) was added followed 5 minutes later by the addition of sodium cyanoboran hydrate (3.35 g, 53.55mmol). Then the solution was heated to reflux for 18 hours. Methanol was evaporated and residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over Mg_2SO_4. Concentration in vacuo gave the cyclopropylamine as an off-white powder (4.9 g, 92.6%).

Part H: To a solution of the cyclopropylamine of part G (4.88 g, 10.95 mmol) in tetrahydrofuran (12.5 mL) and ethanol (12.5 mL) was added NaOH (4.3 g, 100 mmol) in water (25 mL). The solution was then heated to 50-55 degrees Celsius for 12 hours and was stirred at ambient temperature for 18 hours. Solution was acidified to pH=2 and concentration in vacuo provided the acid as white solid together with NaCl in the mixture. To a solution of this mixture in acetonitrile (50 mL) were added O-tetrahydropyronylamine (1.95 g, 16.3 mmol), N-methylmorpholine (2.4 mL, 21.9 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.14 g, 16.3mmol) in sequence. The solution was then stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with H_2O and dried over Mg_2SO_4. Concentration in vacuo provided the tetrehyrdopyronyl (THP) amide as white solid (3.0 g, 53.1%).

Part I: To a solution of the THP amide of part H (3 g, 5.8 mmol) in methanol (45 mL) cooled to zero degrees Celsius was added acetyl chloride (1.5 mL, 21.1 mmol), and the solution was stirred at ambient temperature for 2.5 hours. Vacuum filtration of the precipitate provided hydroxamate HCl salt as a white solid (1.844 g, 68.3%). Analytical calculation for $C_{21}H_{24}N_2O_4S_2$.HCl: C, 53.78; H, 5.37; N, 5.97; S, 13.67. Found: C, 53.40; H, 5.26; N, 5.95; S, 13.68.

Example 33: Preparation of N-hydroxy-1-methyl-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of amine TFA salt of part F, Example 32 (2.67 g, 5.14 mmol) and 37% formaldehyde in aqueous solution (2.0 mL, 25.7 mmol) in methanol (20 mL) was added borane pyridine (2.6 mL, 25.7 mmol) at ambient temperature. The solution was then stirred at ambient temperature for 18 hours. The solution was acidified to destroy excess reagent. Methanol was evaporated and the residue was partitioned between $NaHCO_3$ aqueous solution and ethyl acetate. The $NaHCO_3$ aqueous layer was extracted with ethyl acetate. The combined organic layers were

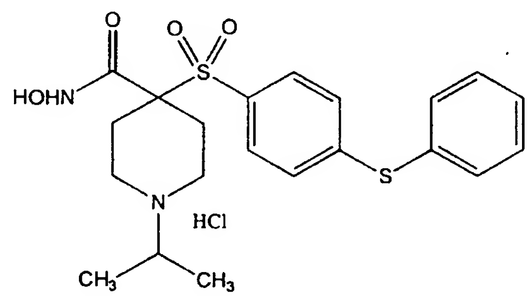
washed with H_2O and dried over Mg_2SO_4. Concentration in vacuo gave the methyl amine as off white foam (1.6 g, 76%).

Part B: To a solution of the methyl amine of part A (1.63 g, 3.88 mmol) in ethanol (20 mL) was added KOH (1.31 g, 23.2 mmol) in water (4 mL), and the resulting solution was heated to 50 degrees Celsius for 8 hours, 70 degree Celsius for 4 hours and stirred at ambient temperature for 18 hours. The solution was acidified and concentrated in vacuo providing the acid as white solid together with NaCl in the mixture. To a solution of this mixture in N,N-dimethylformamide (50 mL) were added O-tetrahydropyronylamine (0.92 g, 7.76 mmol), N-methylmorpholine (1.05 mL, 7.76 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 g, 7.76mmol) in sequence. The solution was stirred at ambient temperature for 72 hours. The solution was concentrated in high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration in vacuo and chromatography (silica, dichloromethane/methanol) provided the THP amide as white solid (0.46 g, 24.2%).

Part C: To a solution of the THP amide of part B (0.22 g, 0.45 mmol) in methanol (5 mL) cooled to zero degrees Celsius was added acetyl chloride (0.096 mL, 13.5 mmol), and the resulting solution was stirred at ambient temperature for 3 hours. The solution was concentrated in vacuo and reverse phase

chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (0.12 g, 60.6%). HSMS calculated for $C_{19}H_{22}N_2O_4S_2$: 407.1099, found 407.1105.

Example 34: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-(phenylthio) phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Into a solution of BOC-sulfone of part E, Example 32 (11.19 g, 22.12 mmol) in ethyl acetate (150 mL) cooled to zero degrees Celsius was bubbled HCl gas for 20 minutes. The solution was stirred at the same temperature for another 40 minutes. Concentration in vacuo and titration with ether provided the amine HCl salt (9.88 g, quantitative yield).

Part B: To a solution of amine HCl salt of part A (4.7 g, 10.6 mmol), triethylamine (2.0 mL, 14.4 mmol) and acetone (2.0 mL, 27.2 mmol) in dichloromethane (100 mL) were added sodium triacetoxylborohydride (5.7 g, 26.9 mmol) followed by acetic acid (1.5 mL, 26.9 mmol) at ambient

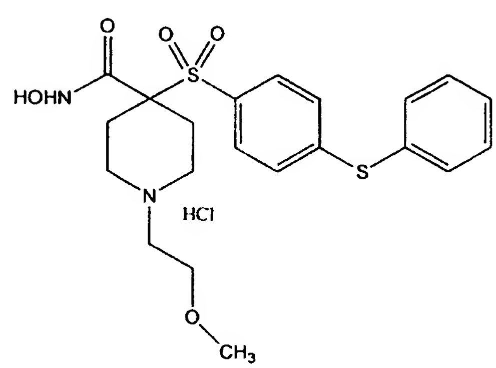
temperature. The solution was stirred for 18 hours and then partitioned in 1N NaOH and ether. The aqueous layer was extracted with ether and combined organic layers were washed with 1N NaOH, H_2O and dried over Mg_2SO_4. Concentration in vacuo gave the isopropyl amine as white foam (4.58 g, 96.2%).

Part C: To a solution of the isopropyl amine of part B (4.58 g, 10.2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added NaOH (2.1 g, 5.25 mmol) in water (20 mL). The solution was heated to 60 degrees Celsius for 13.5 hours, then stirred at ambient temperature for 18 hours. The solution was acidified and concentrated in vacuo providing the acid as white solid together with NaCl in the mixture. To a solution of this mixture in N,N-dimethylformamide (75 mL) were added 1-hydroxybenzotriazole (1.94 g, 14.4 mmol), O-tetrahydropyronylamine (1.8 g, 15.1 mmol), N-methylmorpholine (3.37 mL, 30.7 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.74 g, 14.3mmol) in sequence. The solution was stirred at ambient temperature for 48 hours. The solution was concentrated in high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration in vacuo and chromatography (silica, dichloromethane/methanol) provided the THP amide as white solid (3.78 g, 71.3%).

Part D: To a solution of the THP amide of part C (1.15 g, 2.2 mmol) in methanol (20 mL) was

added acetyl chloride (0.096 mL, 13.5 mmol), and the resulting solution was stirred at ambient temperature for 2.5 hours. The solution was concentrated in vacuo and reverse phase chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (0.69 g, 66.3%). Analytical calculation for $C_{21}H_{26}N_2O_4S_2.HCl.H_2O$: C, 51.58; H, 5.98; N, 5.73; S, 13.11. Found: C, 51.76; H, 5.47; N, 5.72; S, 12.68.

Example 35: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-(phenylthio)phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To the solution of the amine HCl salt of part A, Example 34 (4.3 g, 9.43 mmol) and K_2CO_3 (2.62 g, 19.0 mmol) in N,N-dimethylformamide (40 mL) was added 2-bromoethyl methyl ether (1.9 mL, 20.2 mmol). The solution was stirred at ambient temperature for 48 hours. Then N,N-dimethylformamide was evaporated under high vacuum and the residue was

diluted with ethyl acetate. The organic layer was washed with water and dried over Mg_2SO_4. Concentration in vacuo provided the methoxyl ethyl amine as white foam (4.26 g, 95.3%).

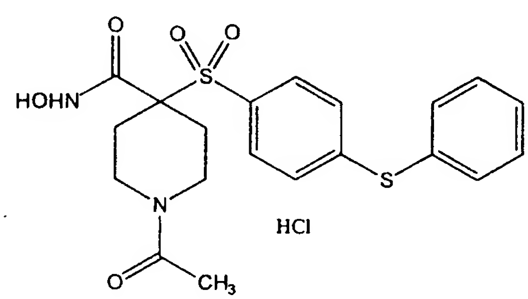
Part B: To a solution of the methoxyl ethyl amine of part A (4.26 g, 9.2 mmol) in tetrahydrofuran (5 mL) and ethanol (5 mL) was added NaOH (3.7 g, 92.5 mmol) in water (9 mL). The solution resulting was heated to 60 degrees Celsius for 12 hours and stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether (2X100 mL) and was acidified to pH=2. Vacuum filtration of the resulting precipitate provided the acid as a while solid (3.5 g, 87.5%).

Part C: To a solution of the acid of part B (3.4 g, 7.8 mmol), also containing N-methyl morpholine (2.6 mL, 23.4 mmol), 1-hydroxybenzotriazole (3.16 g, 23.4 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.85 g, 15.5 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.47 g, 23.4 mmol). The solution was stirred at ambient temperature for 36 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H2O and dried over Mg_2SO_4. Concentration in vacuo provided the amide as off white solid (2.98 g, 71.5%).

Part D: To a solution of the amide of part C (2.98 g, 5.6 mmol) in methanol (40 mL) cooled to

zero degrees Celsius was added acetyl chloride (1.19 mL, 16.8 mmol), and the resulting solution was stirred at the ambient temperature for 3 hours. The solution was concentrated and reverse phase chromatography (on C-18 silica, acetonitrile/H_2O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (2.29 g, 84.6%). Analytical calculation for $C_{21}H_{26}N_2O_6S.HCl.0.9H_2O$: C, 50.12; H, 5.77; N, 5.57; S, 12.74. Found: C, 50.41; H, 5.85; N, 5.73; S, 12.83.

Example 36: <u>Preparation of 1-acetyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride</u>



Part A: To a solution of the phenyl thiophenyl BOC-sulfone of part E, Example 32 (7 g, 1.29 mmol) in tetrahydrofuran (25 mL) and ethanol (25 mL) was added NaOH (5.1 g, 12.9 mmol) in H_2O (50 mL). The solution was heated to reflux for 20 hours. On cooling, the solution was concentrated in vacuo and the dry residue was dissolved in H_2O. The aqueous layer was extracted with ether and was acidified to pH=2 followed by the extraction with ethyl acetate. The combined organic layers were washed again with H_2O

and dried over Mg_2SO_4. Concentration in vacuo provided the BOC-acid as white foam (3.9 g, 60%)

Part B: To a solution of BOC-acid of part A (2.3g, 4.98mmol) in dichloromethane (6 mL) was added trifluroacetic acid (6 mL, 77.8 mmol), and the solution was stirred at ambient temperature for 1 hour. Concentration in vacuo provided the amine as white foam (2.44g, quantitative yield).

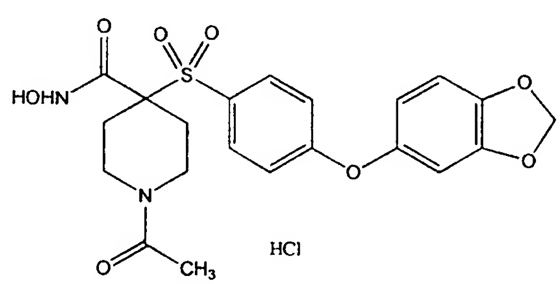
Part C: To a solution of the amine of part B (5.0 g, 12.08 mmol) and triethylamine (8.7 mL, 60.4 mmol) in acetone (20 mL) and H_2O (20 mL) cooled to zero degrees Celsius was added acetyl chloride (4.6 mL, 36 mmol), and the solution was stirred at ambient temperature for 40 hours. The acetone was evaporated and the aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried over Mg_2SO_4. Concentration in vacuo provided the acetyl amide as light yellow foam (5 g, quantitative yield).

Part D: To a solution of acetyl amide of part C (5 g, 11.9 mmol), also containing N-methyl morpholine (5.3 mL, 47.6 mmol), 1-hydroxybenzotriazole (4.8 g, 35.7 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (2.8 g, 23.5 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.8 g, 35.7 mmol), and the solution was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic

layer was washed with saturated $NaHCO_3$, $KHSO_4$, H_2O and dried over Mg_2SO_4. Concentration in vacuo provided the THP amide as white foam (6.07 g, 98.2%).

Part E: To a solution of the THP amide of part D (6.07 g, 11.7 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added acetyl chloride (2.5 mL, 35.1 mmol), and the solution was stirred at ambient temperature for 3 hours. The solution was concentrated and chromatography (on silica, methanol/ dichloromethane) provided hydroxamate HCl salt as a white solid (3.3 g, 65%). Analytical calculation for $C_{24}H_{29}N_3O_6S.HCl.0.9H_2O$: C, 53.36; H, 5.98; N, 7.78. Found: C, 53.61; H, 5.71; N, 7.94. HSMS calculated for $C_{24}H_{29}N_3O_6S$: 488.1855, found 488.1835.

Example 37: Preparation of 1-acetyl-4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of sulfone from Part D, Example 32 (25g, 67.3 mmol) and powdered K_2CO_3 (23.3 g, 16.9 mmol) in N,N-dimethylformamide was added sesamol (23.24 g, 16.8 mmol) at ambient temperature, and solution was heated to ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided sesamol BOC-sulfone as a white foam (33.6 g, 93.6%).

Part B: To a solution of sesamol BOC-sulfone of part E (29.31 g, 54.93 mmol) in ethanol (60 mL) and tetrahydrofuran (60 mL) was added NaOH (21.97 g, 544 mmol) from addition funnel over 20 minutes at ambient temperature. The solution was then heated to sixty degrees Celsius for 9 hours, then ambient temperature for 12 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. It was then extracted with ethyl acetate and the combined organic layers were washed with H_2O and dried over $MgSO_4$. Concentration *in vacuo* provided the acid as white solid (25.3, 91%).

Part C: HCl gas was bubbled into a solution of the acid of part F (20.3 g, 40.15 mmol) in ethyl acetate cooled to zero degrees Celsius. After 1.5 hours, vacuum filtration of white precipitate provided the amine HCl salt as a white solid (16 g, 93.6%).

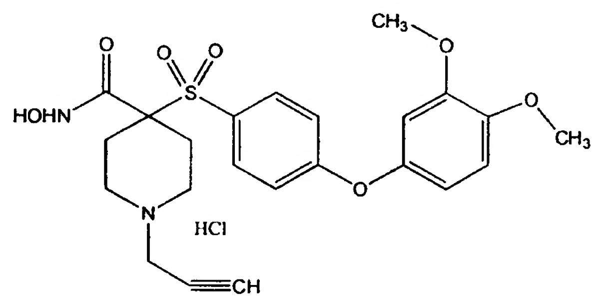
Part D: To the solution of the amine HCl salt of part G (8.1 g, 19.01 mmol) and triethylamine (13.2 mL, 95.05 mmol) in acetone (150 mL) and H_2O (150 mL) cooled to zero degrees Celsius was added acetyl chloride (5.4 mL, 76 mmol). The solution was stirred at ambient temperature for 18 hours. The acetone was evaporated and aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried over Mg_2SO_4. Concentration *in vacuo* provided the acetyl amide as light yellow foam (9.24 g, quantitative yield).

Part E: To the solution of the acetyl amide of part D (9.1 g, 20.33 mmol), N-methyl morpholine (6.7 mL, 61 mmol), 1-hydroxybenzotriazole (8.2 g, 60 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (4.85 g, 40 mmol) in N,N-dimethylformamide (40 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11.65 g, 60 mmol). The resulting solution was stirred at ambient temperature for 20 hours. The solution was then concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, $KHSO_4$, H_2O and dried over Mg_2SO_4. Concentration *in vacuo* and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white a foam (10 g, 89.7%).

Part F: To a solution of 4N HCl in dioxane (20 mL) was added a solution of the amide of part E (5.0 g, 9.1 mmol) in methanol (5 mL) and dioxane (15

mL). That solution was stirred at ambient temperature for 30 minutes. Vacuum filtration of the white precipitate provided the hydroxamate HCl salt as a white solid (3.3 g, 65%). Analytical calculation for $C_{21}H_{22}N_2O_8S.HCl$: C, 54.34; H, 5.15; N, 5.49; S, 6.43. Found: C, 54.54; H, 4.79; N, 6.06; S, 6.93. HSMS calculated for $C_{21}H_{22}N_2O_8S$: 463.1175, found 463.118.

Example 38: Preparation of 4-[[4-(3,4-dimethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: HCl gas was bubbled into a solution of the sulfone of part D, Example 32 (10 g, 24 mmol) in ethyl acetate cooled to zero degrees Celsius. After 4 hours, vacuum filtration of the white precipitate provided the amine HCl salt as a white solid (7.27 g, 86%).

Part B: To a solution of the amine HCl salt of part A (5.98 g, 17 mmol) and powered K_2CO_3 (4.7 g, 34 mmol) in N,N-dimethylformamide (120 mL) was added propargyl bromide (2.022 g, 17 mmol) at

ambient temperature, followed by stirring for 4 hours. The solution was diluted with ethyl acetate and washed with H_2O, saturated NaCl and dried over Mg_2SO_4. Concentration *in vacuo* and chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine as a white solid (5.2 g, 86%).

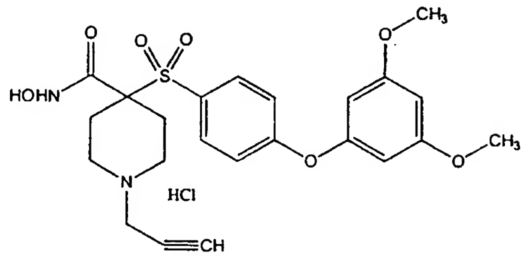
Part C: To a solution of the propargyl amine of part B (8 g, 22.63 mmol) and powdered K_2CO_3 (8.8 g, 56.6 mmol) in N,N-dimethylformamide (150 mL) was added 3,4-dimethoxyphenol (6.98 g, 45 mmol) at ambient temperature. The composition was heated to 90 degrees Celsius for 36 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided phenoxy propargyl amine as light yellow gel (10 g, 90.9%).

Part D: A solution of NaOH (8.2 g, 200 mmol) in H_2O (30 mL) from addition funnel was added to a solution of the phenoxy propargyl amine of part C (10 g, 20.5 mmol) in ethanol (15 mL) and tetrahydrofuran (15 mL) at ambient temperature. The resulting solution was then heated to 60 degrees Celsius for 48 hours and at ambient temperature for 48 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (9.4 g, quantitative yield).

Part E: To a solution of the acid of part D (9.4g, 20.5 mmol), N-methyl morpholine (6.8 mL, 62 mmol), 1-hydroxybenzotriazole (8.3 g, 60 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (4.8 g, 40 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11.7 g, 60 mmol). The resulting solution was then stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration *in vacuo* and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white foam (10 g, 89.7%).

Part F: To a solution of 4N HCl in dioxane (38 mL, 152 mmol)) was added a solution of the amide of part E (8.5 g, 15.2 mmol) in methanol (8 mL) and dioxane (24 mL).The resulting composition was stirred at ambient temperature for 80 minutes. Concentration *in vacuo* and titration with ether provided hydroxamate HCl salt as a white solid (7.7 g, quantitative yield). HSMS calculated for $C_{23}H_{26}N_2O_7S$: 475.1461, found 475.1539.

Example 39: Preparation of 4-[[4-(3,5-dimethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-<u>piperidinecarboxamide, monohydrochloride</u>



Part A: To a solution of the propargyl amine of Part B, Example 38 (2 g, 5.6 mmol) and powdered K_2CO_3 (1.9 g, 13.7 mmol) in N,N-dimethylformamide (20 mL) was added 3,5-dimethoxyphenol (2.18 g, 13.7 mmol) at ambient temperature. The resulting composition was heated to 90 degrees Celsius for 36 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided phenoxy propargyl amine as light yellow gel (2.76 g, quantitative yield).

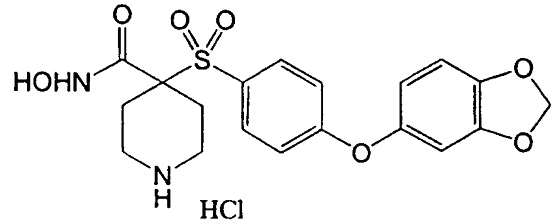
Part B: To a solution of the phenoxy propargyl amine of part A (2.75 g, 5.6 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was added NaOH (2.3 g, 56 mmol) in H_2O (10 mL) at ambient temperature. The solution was then heated to 60 degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of white precipitate provided the acid as white solid (2 g, 77.2%).

Part C: To a solution of the acid of part B (2 g, 4.3 mmol), also containing N-methyl

morpholine (1.9 mL, 17.2 mmol), 1-hydroxybenzotriazole (1.74 g, 13.2 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (1.02 g, 8.6 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.47 g, 12.9 mmol). The resulting composition was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration *in vacuo* and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white foam (2.4 g, quantitative yield).

Part D: To a solution of 4N HCl in dioxane (13 mL, 52 mmol)) was added a solution of the THP amide of part C (2.43 g, 4.35 mmol) in methanol (2 mL) and dioxane (6 mL), and the composition was stirred at ambient temperature for 80 minutes. Vacuum filtration of the precipitate and washing with ether provided the hydroxamate HCl salt as a white solid (1.25 g, 56.3%). Analytical calculation for $C_{23}H_{26}N_2O_7S.1.5HCl$: C, 52.20; H, 5.24; N, 5.29. Found: C, 52.00; H, 5.05; N, 5.17.

Example 40: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride

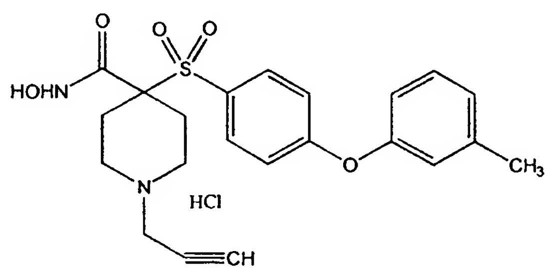


Part A: To a solution of the N-BOC carboxylic acid compound of part B, Example 37 (1.25 g, 2.47 mmol), N-methylmorpholine (1.00 g, 9.89 mmol) and 1-hydroxybenzotriazole hydrate (0.40 g, 2.96 mmol) in N,N-dimethylformamide (8 mL) at ambient temperature was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.616 g, 3.21 mmol). After 5 minutes a solution of O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.39 g, 3.33 mmol) in N,N-dimethylformamide (2 mL) was added. After 2 days the pale yellow solution was concentrated *in vacuo* to afford a residue which was dissolved in ethyl acetate and washed successively with water (3X) and brine and dried over sodium sulfate. Concentration afforded a residue that was chromatographed on silica gel eluting with ethyl acetate/hexane (20/80) to afford the THP-protected hydroxamate as an oil (1.54 g, 100%).

Part B: To a solution of THP-protected hydroxamate of part A (1.49 g, 2.46 mmol) in dioxane (9 mL) and methanol (3 mL) was added 4 N HCl in dioxane (10 mL, 40 mmol). After 1.5 hours at ambient temperature the suspension was treated with diethyl ether (15 mL) and filtered to afford the title hydroxamate (1.00 g, 89%) as a colorless powder. MS

(CI) MH^+ calculated for $C_{19}H_{20}N_2SO_7$: 421, found 421. Analytical calculation for $C_{19}H_{20}N_2SO_7.HCl$: C, 49.95; H, 4.63; N, 6.13; Cl, 7.76; S, 7.02. Found: C, 49.82; H, 4.60; N, 5.98; Cl, 17.38; S, 7.10.

Example 41: Preparation of N-hydroxy-4-[[4-(3-methylphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of propargylamine of part F, Example 9 (8.0 gm, 22.6 mmol) and K_2CO_3 in N,N-dimethylformamide (30 mL) was added m-cresol (3.5 g, 33.9 mmol) and the solution was stirred at 90 degrees Celsius for 18 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, eluting with 10% ethyl acetate/hexane) provided the 3-methyl phenoxyphenyl compound as a solid (10.3 g, 98%). Cal'd MS for $C_{24}H_{28}NSO_5$ 441.1688, found 442.1697

Part B: To a solution of 3-methyl phenoxyphenyl compound of part A (10.3 g, 22.0 mmol) in tetrahydrofuran (50 mL) and ethanol (50 mL) was

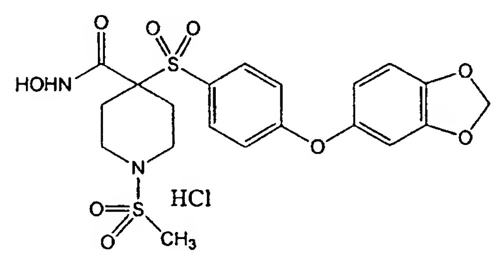
added NaOH (8.9 g, 22.3 mol) and the solution was heated at 65 degrees Celsius for 24 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3. Vacuum filtration of the resulting precipitate provided the acid as a white solid (9.0 g, 91%). MS cal'd for $C_{22}H_{24}NSO_5$ = 414.1375. Found = 414.1389.

Part C: To a solution of the acid of part B (9.0 g, 19.5 mmol) was added 1-hydroxybenzotriazole (3.24 g, 23.9 mmol), N-methylmorpholine (6.58 mL, 59.9 mmol), O-tetrahydro-2H-pyran-yl-hydroxylamine (3.5 g, 29.9 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodimmide hydrochloride (5.35 g, 27.9 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, eluting with 40% ethyl acetate/hexane) provided the desired THP-protected hydroxamate as a solid (6.9 g, 67%). Analytical calculation for $C_{27}H_{33}N_2SO_6$:0.1 H_2O: C, 62.92, H, 6.49, N, 5.43, S, 6.23. Found: C, 62.69, H, 6.47, N, 5.57, S, 6.33. Cal'd MS for $C_{27}H_{33}N_2SO_6$: 513.2059. Found 513.2071.

Part D: To a solution of THP-protected hydroxamate of part C (6.4 gm, 12.5 mmol) in dioxane (56 mL) and methanol (19 mL) was added 4 N HCl/dioxane (40 mL). After stirring at ambient temperature for 1 hours, the solution was concentrated *in vacuo*. Trituration with ethyl ether

provided the title compound as a white solid (5.66 g, 97.4%). Cal'd MS for $C_{22}H_{24}N_2SO_5$+1: 429.1484.. Found M+1: 429.1493

Example 42: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-1-(methylsulfonyl)-4-piperidinecarboxamide



Part A: To a solution of sulfone of part D, Example 32 (25.g, 67.3 mmol) in N,N-dimethylformamide was added potassium carbonate (23.3 g, 0.169 mol) and sesamol (23.2 g, 0.164 mol). The solution was submerged in an oil bath at 90°C and stirred for 25 hours. Ethyl acetate was added to the solution, and the organic phase was washed with water, 1N NaOH and water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Chromatography on silica, eluting with ethyl acetate/hexane (15/85) provided the ethyl ester compound as an oil (29.3 g, 82%).

Part B: To a solution of ethyl ester from part A (29.3 gm, 54.93 mmol) in ethanol (60 mL) and tetrahydrofuran (60 mL) was added a solution of NaOH (21.9 g, 0.549 mol) in water 120 mL) and the solution was heated at 65 degrees Celsius for 10 hours. The

solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3. The solution was extracted with ethyl acetate. The solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the acid as a yellow foam (25.6 g 92.1%).

Part C: To a solution of the acid of Part B (20.3 g, 40.15 mmol) in ethyl acetate at zero degrees C was bubbled gas HCl for 20 minutes. The solution stirred at Zero degrees Celsius for 1.5 hours. The precipitate formed was filtered and washed with ether to give the amine hydrochloride as a white solid (16.0 g, 93.5%)

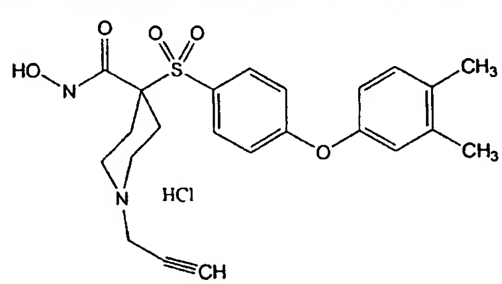
Part D: To a solution of amine hydrochloride of part C (7.5g, 17.0 mmol) in methylene chloride (200 mL) was added methanesulfonyl chloride (2.0 g, 25.0 mol) and the solution was stirred at ambient temperature for 18 hours. The solution was washed with water and saturated NaCl, dried over magnesium sulfate, concentrated *in vacuo* to provide the acid as a white solid (6.97g, 85%).

Part E: To a solution of the acid of part D (7.37 g, 15.0 mmol) was added 1-hydroxybenzotriazole (2.43 g, 18.0 mmol), N-methylmorpholine (4.94 mL, 45.0 mmol), O-tetrahydro-2H-pyran-yl-hydroxylamine (2.65 g, 22.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodimmide hydrochloride (4.02 g, 21.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer

was washed with saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, eluting with 50% ethyl acetate/hexane) provided the desired THP-protected hydroxamate as a solid (7.54 g, 85%).

Part F: To a solution of THP-protected hydroxamate of part E (6.32 gm, 10.8 mmol) in dioxane (75 mL) and methanol (25 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 1 hour, the solution was concentrated *in vacuo*. Trituration with ethyl ether provided the title compound. Chromatography (on silica, 5% methanol/ethyl acetate) provided the hydroxamate as a white solid (4.32 g, 80%) Cal'd MS for $C_{22}H_{22}N_2S_2O_9$+1: 499.0845. Found 499.0848.

Example 43: Preparation of 4-[[4-(3,4-Dimethylphenoxyl)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monhydrochloride



Part A: A mixture of the fluoro compound from part F, Example 9 (2.0 g, 5.66 mmol), 3,4-dimethylphenol (2.0 g, 16.5 mmol), and potassium carbonate (2.3 g, 16.5 mmol) in N,N-dimethylformamide (15 mL) was heated at 90 degrees Celsius overnight

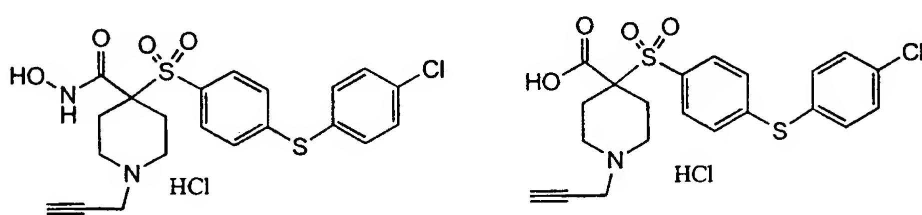
(about 18 hours) under an atmosphere of nitrogen. The brown mixture was concentrated *in vacuo* and purified by chromatography (on silica, ethyl acetate/hexane) to afford the 3,4-dimethylphenoxy phenyl compound as a clear, yellow oil (2.0 g, 79% yield). Analytical calculation for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N, 3.04; S, 7.04. Found: C, 65.76; H, 6.37; N, 3.03; S, 7.00.

Part B: A solution of the 3,4-dimethylphenoxy phenyl compound of part A (2.0, 4.93 mmol) and potassium hydroxide (1.7 g, 29.7 mmol) in a mixture of ethanol (25 mL) and water (4 mL) was stirred at reflux for four hours under a nitrogen atmosphere. The solution was cooled with an ice bath, subsequently acidified with concentrated hydrochloric acid, and concentrated to a crude residue. The crude residue, O-tetrahydo-2H-pyran-2-yl-hydroxylamine (0.88 g, 7.50 mmol), triethylamine (0.81 mL, 5.81 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in acetonitrile (24 mL) was stirred at ambient temperature overnight. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, a saturated sodium bicarbonate solution, water, and a saturated salt solution. After drying over magnesium sulfate, the filtrate, as the THP-protected hydroxamate, was concentrated to a yellow foam.

Part C: The THP-protected hydroxamate (920 mg, 1.75 mmol) o f part B was dissolved in methanol (16 mL). Acetyl chloride (0.37 mL, 5.3 mmol) was

added. After three hours, concentration followed by reverse phase HPLC afforded the title compound as a white solid (611 mg, 79%). MS (EI) MH^+ calculated for $C_{23}H_{26}N_2O_5S$: 443, found 443.

Example 44: Preparation of 4-[[4-(4-chlorophenyl)thiolphenyl]sulfonyl]-1-(propynyl)-4-piperidinecarboxylic acid, monohydrochloride and 4-[[4-(4-chlorophenyl)thiolphenyl]sulfonyl]-N-hydroxy-1-(propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: A mixture of the fluoro compound from part F, Example 9 (2.0 g, 5.66 mmol), 4-chlorothiophenol (1.0 g, 6.94 mmol), and potassium carbonate (1.1 g, 8.00 mmol) in N,N-dimethylformamide (12 mL) was stirred overnight (about 18 hours) under an atmosphere of nitrogen at ambient temperature. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and a saturated salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to a yellow oil.

The oil was purified by chromatography (on silica, ethyl acetate/hexane) to afford the 4-chlorophenylthiolphenyl compound as a white solid (2.0 g, 75% yield). Analytical calculation for $C_{23}H_{24}NO_4S_2C_1$: C, 57.791; H, 5.06; N, 2.93; S, 13.42; Cl, 7.42. Found: C, 57.57; H, 5.11; N, 2.94; S, 13.19; Cl, 7.73.

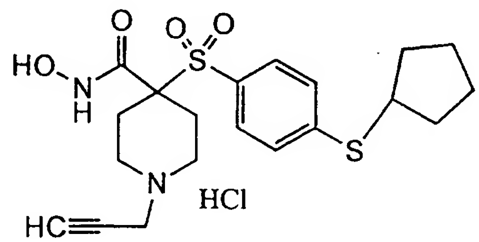
Part B: The chorophenylthiophenyl compound from part A (2.04 g, 4.27 mmol) was diluted with ethanol (30 mL) and water (5mL). Potassium hydroxide (1.55 g, 27.7 mmol) was added, and the mixture was heated at reflux for 3 hours. After complete reaction, the solution was cooled and was acidified to pH=1-3 with concentrated HCl. The solvent was removed by rotary evaporation and the residue was azeotroped to dryness by repeated addition of acetonitrile. The acid hydrochloride was further dried on a vacuum line, then carried as is through the coupling reaction. The saponification was presumed to be quantitative.

Part C: The carboxylic acid hydrochloride from the previous step (4.27 mmol) was suspended in acetonitrile (20 mL). N-Methylmorpholine (about 1.0 mL) was added, followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (585 mg, 5 mmol). After 5 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 955 mg, 5 mmol) was added. The mixture was stirred overnight (about 18 hours), then solvent was removed by rotary evaporation, the residue was diluted with half-saturated $NaHCO_3$ solution (50 mL), and the product was extracted into

ethyl acetate (2 X100 mL). In this example, an intractable emulsion complicated compound recovery. The combined organic layers were dried over $MgSO_4$, filtered through silica, concentrated, and subjected to chromatography (flash silica, ethyl acetate/hexane) affording, on concentration, the title O-THP-protected hydroxamate (162 mg, 7%, from ester) as a foam. MS (EI) MH^+ calculated for $C_{21}H_{22}N_2O_4S_2Cl$: 450, found 450. Because mass recovery was poor, the silica filter cake was extracted with 1:1 methanol:ethyl actetate affording 4-[[4-(4-chlorophenyl)thiolphenyl]sulfonyl]-1-(propynyl)-4-piperidinecarboxylic acid, monohydrochloride (540 mg, 26%)

Part D: The O-THP-protected hydroxamate of part C (441 mg, 0.80 mmol) was dissolved in methanol (2 mL). Acetyl chloride (0.2 mL, 3 mmol) was added. After three hours, concentration followed by reverse phase HPLC afforded the title hydroxamate compound as a pink solid (162 mg, 44%). MS (EI) MH^+ calculated for $C_{21}H_{22}N_2O_4S_2$: 465, found 465.

Example 45: Preparation of 4-[[4-(Cyclopentylthio)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



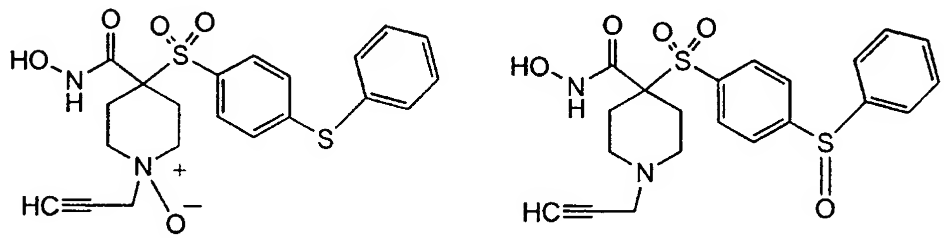
Part A: The propargyl amine of part F, Example 9 (3.05 g, 8.5 mmol) was combined with K_2CO_3 (1.38 g, 10 mmol), N,N-dimethylformamide (6 mL) and cyclopentyl mercaptan (1.02 mL, 10 mmol). The mixture was heated to 80 degrees Celsius for 4 hours and 95 degrees Celsius for 2.5 hours, monitoring by TLC. Aqueous workup was accomplished using water (10 mL) and ethyl acetate (2 X 100 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed (flash silica; ethyl acetate/hexane eluant) affording the cyclopentylmercaptyl compound as an oil (3.2 g, 86%)

Part B: The cyclopentylmercaptyl compound from part A (3.12 g 7.13 mmol) was diluted with ethanol (50 mL) and water (8 mL). Potassium hydroxide (2.59 g, 46.3 mmol) was added, and the mixture was heated at reflux for 3.5 hours. After complete reaction, the solution was cooled and was acidified to pH=1-3 with concentrated HCl. The solvent was removed by rotary evaporation and the residue was azeotroped to dryness by repeated addition of acetonitrile. The carboxylic acid hydrochloride was further dried on a vacuum line, then carried as is through the coupling reaction. The saponification was presumed to be quantitative.

Part C: The carboxylic acid hydrochloride from Part B (7.13 mmol) was suspended in acetonitrile (50 mL). N-Methylmorpholine (ca. 2.0 mL) was added, followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.05 g, 9 mmol). After 5 minutes, EDC (1.72 g, 9 mmol) was added. The mixture was stirred overnight (about 18 hours), then solvent was removed by rotary evaporation. The residue was diluted with half-saturated $NaHCO_3$ solution (50 mL), and the product was extracted into ethyl acetate (2 X100 mL). The combined organic layers were dried over $MgSO_4$, filtered through silica, concentrated, and subjected to chromatography (flash siilca, ethyl acetate/hexane) affording, on concentration, the O-THP-protected hydroxamate (2.0 g, 51%, from ester) as a foam.

Part D: The O-THP-protected hydroxamate from Part D (2.00 g, 3.95 mmol) was dissolved in methanol (16 mL). Acetyl chloride (0.86 mL, 12 mmol) was added over 2 minutes. The reaction was stirred at ambient temperature for 4 hours, then concentrated, with repeated addition of chloroform and acetonitrile to effect drying. The title compound precipitated as a white solid (1.77 g, 98%). MS (EI) MH^+ calculated for $C_{20}H_{26}N_2O_4S_2$: 422, found 422.

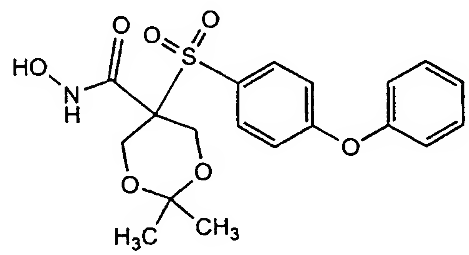
Example 47: Preparation of N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, 1-oxide and N-hydroxy-4-[[4-(phenylsulfinyl)-phenyl]sulfonyl-1-(2-propynyl)-4-piperidinecarboxamide



m-Chloroperbenzoic acid (57-86%, 120 mg) was added to a solution of N-hydroxy-4-[[4-(phenylthio)phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide (title compound, Example 9)(215 mg, 0.5 mmol) in methanol (5 mL) at zero degrees Celsius. The reaction was permitted to warm slowly to ambient temperature and after 16 hours, the mixture was passed through a micron filter and concentrated. Reverse phase HPLC (Delta Pak 50 X 300 mm; 15 micron C_{18} 100 Angstrom; 30 minute gradient method starting with dilute HCl (0.5 mL/4 L): acetonitrile 80:20, ending with 50:50) separated 5 major components. The first and second peaks off the column afforded, upon concentration, 14 (6%) and 16 mg (7%) of two compounds, which were assigned as diastereomers of N-Hydroxy-4-[[4-(phenylsulfinyl)-phenyl]sulfonyl-1-(2-propynyl)-4-piperidinecarboxamide on the basis of their NMR

spectra. The third peak was unidentified. The 4th peak was assigned by NMR as N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, 1-oxide (147 mg, 66%) MS (EI) MH^+ calculated for $C_{21}H_{22}N_2O_5S_2$: 447, found 447. The last peak contained 73 mg of recovered 3-chlorobenzoic acid.

Example 48: Preparation of N-hydroxy-2,2-dimethyl-5-[(4-phenoxyphenyl)sulfonyl]-1,3-dioxane-4-carboxamide



Part A: A fresh sodium methoxide solution was prepared by slowly adding hexane-washed sodium spheres (9.4 g, 410 mmol) to methanol (1.0 L) at zero degrees Celcius. To this cooled solution was added the 4-fluorothiophenol (50.0 g, 390 mmol) followed by methyl 2-chloro acetate (42.3 g, 390 mmol). After warming to ambient temperature the reaction was stirred overnight (about 18 hours). The methanol was removed *in vacuo* and the residue was taken up in ethyl acetate (300 mL). The organic layer was washed with water (2x-200 mL) and dried over $MgSO_4$.

Concentrating afforded the methyl ester sulfide product as a clear oil (71.8 g, 92%).

Part B: To a solution of the methyl ester sulfide product of part A (71.8 g, 358 mmol) in 70% methanol/H_2O (1.0 L) was slowly added Oxone™ (660 g, 1.08 mol). The mixture stirred overnight (about 18 hours) at ambient temperature. The excess Oxone™ was filtered off and the methanol was removed from the filtrate *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate (3x 300 mL). The organic layers were washed with water (2x-300 mL) and dried over $MgSO_4$. Concentrating afforded the sulfone product as a tan oil (82 g, 98%).

Part C: To a prepared slurry of potassium bicarbonate (1.0 g, 9.8 mmol) in 37% formaldehyde solution was added the sulfone product of part B (28.6 g, 123 mmol). The reaction was stirred for one hour and then a saturated solution of sodium sulfate (20 mL) was added. After stirring for thirty minutes, the mixture was extracted with diethyl ether (4x-100 mL). The organic layers were dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone diol product as a clear oil (15.3 g, 42%).

Part D: The sulfone diol product of Part C (1.3 g, 4.5 mmol) was dissolved in acetone (40 mL) along with 2,2-dimethoxypropane (1.1 mL, 9.0 mmol) and p-toluenesulfonic acid monohydrate (0.03 mg, 0.14 mmol) and the resulting composition was refluxed for 6 hours. After cooling, the mixture was neutralized with solid Na_2CO_3 (pH~7), filtered, and concentrated.

The residue was dissolved in chloroform (50 mL) and washed with water (2x-30 mL). Drying over $MgSO_4$ and concentrating gave the dimethyl ketal product as an opaque oil (1.4 g, 94%).

Part E: Phenol (0.6 g, 6.3 mmol) and cesium carbonate (2.0g, 6.3 mmol) were added to a solution of the dimethyl ketal product (1.4 g, 4.2 mmol) of part D in N,N-dimethylformamide (20 mL). The mixture was heated at 90 degrees Celsius for five hours, diluted with water (20mL), and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with brine (1x-100 mL) and water (1x-100 mL). Concentrating afforded the phenol-O-phenol dimethyl ketal as a dark brown oil (1.51 g, 88%).

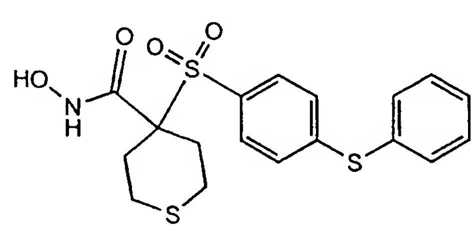
Part F: To a solution of the phenol-O-phenol dimethyl ketal product (1.5 g, 3.4 mmol) of part E in tetrahydrofuran (10 mL) was added an aqueous lithium hydroxide solution (0.34 g, 14.8 mmol, in 5 mL of H_2O). The reaction was stirred for two hours and then was diluted with water (15 mL) and acidified via 30% HCl_{aq} to pH=3. The acidic solution was extracted with diethyl ether (3x-100 mL). Drying over $MgSO_4$ and concentrating afforded the carboxylic acid product as a brown oil (1.5 g, quantitative yield).

Part G: To a solution of the carboxylic acid product of Part F (1.3 g, 3.3 mmol) and N-hydroxybenzotriazole hydrate (0.54g, 4.0 mmol) in DMF (15 mL) was added 4-methylmorpholine (1.67 g, 16.5 mmol), O-tetrahrdro-2H-pyran-2-yl-hydroxylamine (1.2 g, 10.2 mmol), and EDC (0.88 g, 4.6 mmol),

respectively. After stirring overnight, the DMF was removed *in vacuo* and the residue was taken up in ethyl acetate/water (1:1, 50 mL). The organic layer was washed with brine (1x-20 mL) and water (1x-20 mL) and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the THP-protected hydroxylamine product as a white solid (0.36 g, 22%) as well as the decarboxylated by-product (0.27 g, 24%).

Part H: To a solution of the THP-protected hydroxylamine product of Part G (0.36 g, 0.73 mmol) in dioxane (3 mL) and methanol (1mL) was added 4 N HCl in dioxane (2 mL). The reaction was stirred for five minutes and then the solvents were removed *in vacuo*. Chromatography (reverse phase C-18, acetonitrile/water) gave the title compound as a white solid (0.13 g, 44%). MS (FAB) M^+H calculated for $C_{19}H_{21}NO_7S$: 408, found 408.

Example 49: Preparation of tetrahydro-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-2H-thiopyran-4-carboxamide



Part A: To a solution of methyl 2-chloroacetate (322 g, 2.96 mol) in N,N-

dimethylacetamide(1.0 L) were added thiophenol (400 g, 3.12 mol) and potassium carbonate (408 g, 2.96 mol). The reaction was stirred at ambient temperature overnight(about 18 hours). After diluting with a minimal amount of water (800 mL), the mixture was extracted with ethyl acetate (4x-1L). The organic layers were washed with water (1x-800 mL), dried over $MgSO_4$, and concentrated to afford the sulfide product as a clear oil (614 g, quantitative yield).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) was added water (100 mL) and Oxone®(720 g, 1.17 mol) at twenty degrees Celsius. An exotherm to 67 degrees Celsius was noted. After two hours, the reaction was filtered and the cake washed well with methanol. The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone of part B (60.0 g, 258 mmol) in DMA (350 mL) was added the dibromoethylthioether (76.9 g, 310 mmol), followed by potassium carbonate (78.3 g,568 mmol). The mixture was stirred five minutes before adding catalytic amounts of 4-dimethylaminopyridine and tetrabutylammonium bromide. The reaction was stirred overnight (about 18 hours), after which it was poured into a stirring solution of 10% HCl_{aq} (2.5 L). The resulting precipitate was filtered and washed with

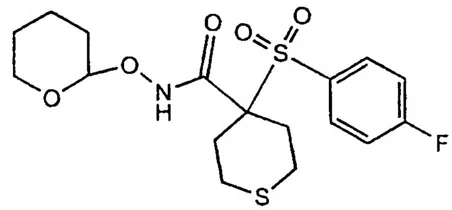
hexane to remove the excess thioether. Drying *in vacuo* overnight (about 18 hours) yielded the methylester thiopyran -Ph-p-F as a yellow powder (76.1 g, 93%).

Step D: To a solution of the methylester thiopyran -Ph-p-F of part C (4.0 g, 12.6 mmol) in N,N-dimethylacetamide (25 mL) were added cesium carbonate (6.1 g, 18.9 mmol) and thiophenol (2.1 g, 18.9 mmol). The mixture was stirred 2 hours at 90 degrees Celsius. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3x-100 mL). The organic layers were washed with brine (1x-75 mL) and water (1x-75 mL) and was then dried over $MgSO_4$. Chromatography (on silica, ethyl acetate / hexane) provided the phenyl-S-phenyl methyl ester as a yellowish solid (3.6 g, 71%).

Step E: Potassium trimethylsilonate (1.24 g, 9.7 mmol) was added to a solution of the phenyl-S-phenyl methyl ester of part D (3.6 g, 8.8 mmol) in tetrahydrofuran (15 mL). The mixture was stirred 2-3 hours at ambient temperature or until a solid precipitate developed. After the hydrolysis was complete, N-methylmorpholine (2.9 mL, 26.4 mmol) was added followed by PyBrop (4.9 g, 10.6 mmol). The solution was stirred for 10 minutes. Aqueous hydroxylamine (0.32 g, 9.7 mmol) was added and the mixture stirred for an additional 2 hours. After completion, the solvent was removed *in vacuo*. Chromatography (reverse phase C-18, acetonitrile / water) of the residue provided the title compound as

an off white solid (0.82 g, 23%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{19}NO_4S_3$: 410, found 410.

Example 50: Preparation of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-thiopyran-4-carboxamide



Part A: Thiophenol (400 g, 3.12 mol) and potassium carbonate (408 g, 2.96 mol) were added to a solution of methyl 2-chloroacetate (322 g, 2.96 mol) in N,N-dimethylacetamide (1.0 L). The reaction was stirred at ambient temperature overnight (about 18 hours). After diluting with a minimal amount of water (800 mL), the mixture was extracted with ethyl acetate (4x-1L). The organic layers were washed with water (1x-800 mL), dried over $MgSO_4$, and concentrated to afford the sulfide product as a clear oil (614 g, quantitative yield).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) was added water (100 mL) and Oxone® (720 g, 1.17 mol) at 20 degrees Celsius. An exotherm to 67 degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with methanol.

The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the methyl ester sulfone as a crystalline solid (82.74 g, 94%).

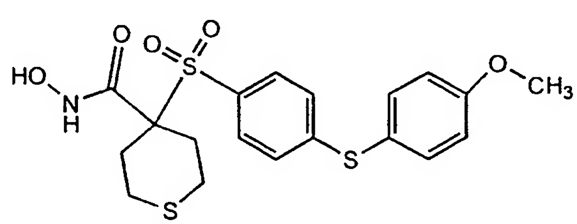
Part C: To a solution of the methyl ester sulfone product of part B (60.0 g, 258 mmol) in N,N-dimethylacetamide (350 mL) was added 2,2-dibromoethylthioether (76.9 g, 310 mmol) followed by potassium carbonate (78.3 g,568 mmol). The mixture was stirred five minutes before adding catalytic amounts of 4-dimethylaminopyridine and tetrabutylammonium bromide. The reaction was stirred overnight (about 18 hours), after which it was poured into a stirring solution of 10% HCl_{aq} (2.5 L). The resulting precipitate was filtered and washed with hexane to remove the excess thioether. Drying *in vacuo* overnight (about 18 hours) yielded the thiopyran methyl ester as a yellow powder (76.1 g, 93%).

Step D: To a solution of the thiopyran methyl ester of part C (30.0 g, 94 mmol) in tetrahydrofuran (250 mL) was added potassium trimethylsilonate (28.9 g, 226 mmol). The mixture was stirred 2-3 hours at ambient temperature or until a solid precipitate developed. After the hydrolysis was complete, the solvent was removed *in vacuo*. Water (200 mL) was added and the mixture was washed with diethyl ether (1x-200 mL). The aqueous layer was cooled to zero degrees Celsius and 10% HCl_{aq} was slowly added until a precipitate formed. The solid

was collected and dried *in vacuo* with phosphorous pentoxide to afford the thiopyran carboxylic acid as a yellow solid (17.8 g, 62%).

Part E: To a solution of the thiopyran carboxylic acid of part D (17.8 g, 58.5 mmol) in N,N-dimethylformamide (100 mL) was added N-methylmorpholine (19.3 mL, 176 mmol) followed by N-hydroxybenzotriazole hydrate(9.5 g, 70.2 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (10.3 g, 87.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16.8 g, 87.8 mmol). The mixture was stirred three hours and was then diluted with water (100 mL). The mixture was extracted with ethyl acetate (4x-200 mL). Organic layers were washed with an aqueous saturated potassium carbonate solution (1x-200 mL), 1% HCl_{aq}, and brine (1x- 200 mL). Drying over $MgSO_4$ and concentrating *in vacuo* afforded the title compound as an off white solid (30.8 g, quantitative yield). MS (FAB) M^+H calculated for $C_{17}H_{22}FNO_5S_2$: 404, found 404.

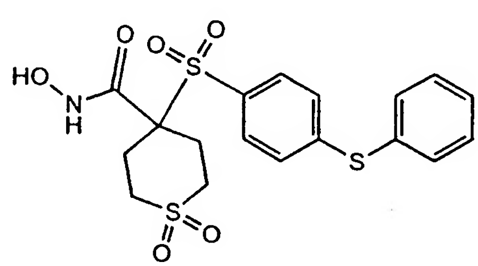
Example 51: Preparation of Tetrahydro-N-hydroxy-4-[[4-[(4-methoxypheny)thio]phenyl]sulfonyl]-2H-thiopyran-4-carboxamide



Part A: To a solution of the title compound of Example 50 (6.0 g, 14.9 mmol) in N,N-dimethylacetamide (25mL) was added 4-methoxy thiophenol (2.5 g, 17.8 mL), followed by potassium carbonate (6.2 g, 44.7 mmol). The reaction was heated at 60 degrees Celsius for three hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over $MgSO_4$. Concentrating *in vacuo* provided the THP-protected - Phenyl -S- pPhenyl-OMe product as a yellowish solid (9.2 g, quantitative yield).

Part B: To a solution of the THP-protected - Phenyl -S- pPhenyl-OMe product from part A (9.2 g, 14.9 mmol) in dioxane was slowly added 4N HCl in dioxane (10 mL). After stirring overnight (about 18 hours), the solvent was removed. Chromatography on the resultant residue (reverse phase C-18, acetonitrile/water) gave the title compound as a white solid (1.84 g, 28.3%). MS (FAB) M^+H calculated for $C_{19}H_{21}NO_5S_3$: 440, found 440.

Example 52: Preparation of Tetrahydro-N-hydroxy-4-[(4-phenylthio)phenyl]sulfonyl]-2H-thiopyran-4-carboxamide 1,1-dioxide

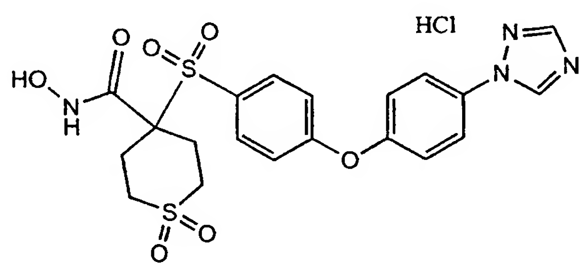


Part A: To a solution of the title compound of Example 50 (13.0 g, 24.5 mmol) in methylene chloride(100 mL) cooled to zero degrees Celsius was slowly added 50-60% m-chloroperbenzoic acid (17.1 g, 49.5 mmol). The mixture was stirred one hour at zero degrees Celsius followed by an additional 3 hours as the temperature rose to ambient conditions. Water (200 mL) was added and the mixture was neutralized with 10% ammonium hydroxide (100 mL). The organic layer was washed with water (1x-200 mL) and dried over $MgSO_4$. Concentrating *in vacuo* provided an orangish oil (3.5 g, 33%). The water/10% ammonium hydroxide solution was saturated with sodium chloride and extracted with ethyl acetate (2x-400 mL). Organic layer was dried over $MgSO_4$ and concentrated to afford the THP-protected sulfone-thiopyran-p-F compound as an orange foam (6.1 g, 57%).

Part B: To a solution of the THP-protected sulfone-thiopyran-p-F from Part A (9.6 g, 22 mmol) in N,N-diemthylacetamide (120mL) was added thiophenol (2.9 g, 26.4 mL), followed by potassium carbonate (9.1 g, 66 mmol). The reaction was heated at 60 degrees Celsius for four hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the THP-protected -phenyl-S-phenyl product as an orange oil (5.1 g, 43%).

Part C: To a solution of the THP-protected -phenyl-S-phenyl product from part B (5.1 g, 9.4 mmol) in dioxane was slowly added 4N HCl in dioxane (10 mL). After stirring overnight (about 18 hours), the solvent was removed. Chromatography of the resultant residue (reverse phase C-18, acetonitrile/water) gave the title compound as a pink solid (1.2 g, 29%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{19}NO_6S_3$: 442, found 442.

Example 53: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-(1H-1,2,4-triazol-1-yl) phenoxy]-phenyl]-sulfonyl]-2H-thiopyran-4-carboxamide 1,1-dioxide, monohydrochloride



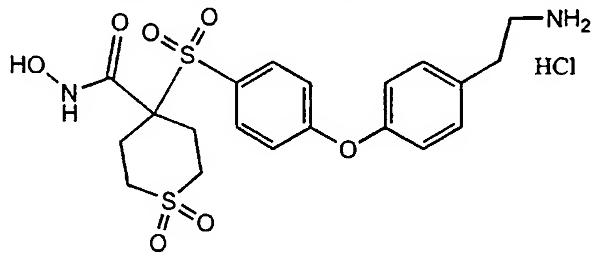
Part A: To a solution of the title compound of Example 50 (13.0 g, 24.5 mmol) in methylene chloride (100 mL) cooled to zero degrees Celsius was slowly added 50-60% m-chloroperbenzoic acid (17.1 g, 49.5 mmol). The mixture was stirred one hour at zero degrees Celsius followed by an additional 3 hours as the temperature rose to ambient conditions. Water (200 mL) was added and the mixture was neutralized with 10% ammonium hydroxide (100 mL). The organic

layer was washed with water (1x-200 mL) and dried over $MgSO_4$. Concentrating *in vacuo* provided an orangish oil (3.5 g, 33%). The water/10% ammonium hydroxide solution was saturated with sodium chloride and extracted with ethyl acetate (2x-400 mL). Organic layer was dried over $MgSO_4$ and concentrated to afford the THP-protected sulfone-thiopyran-p-F as an orange foam (6.1 g, 57%).

Part B: To a solution of the THP-protected sulfone-thiopyran-p-F from A (6.0 g, 13.8 mmol) in N,N-dimethylformamide (25 mL) was added 4-(1H-1,2,4-triazol-1-yl)phenol (4.4 g, 27.5 mmol), followed by cesium carbonate (13.4 g, 41.4 mmol). The reaction was heated at 95 degrees Celsius for five hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over $MgSO_4$. Concentrating afforded the THP-protected phenyl-O-phenyl triazole product as a tan solid (9.7 g, quantitative yield).

Part C: To a solution of the crude THP-protected phenyl-O-phenyl triazole product from B (8.0 g, 13.8 mmol) in acetonitrile (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a tan solid (1.3 g, 18%). MS (FAB) $M^{+}H$ calculated for $C_{20}H_{21}ClN_4O_7S_2$: 493, found 493.

Example 54: Preparation of 4-[[4-[4-(2-aminoethyl))-phenoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-thiopyran-4-carboxamide 1,1-dioxide monohydrochloride



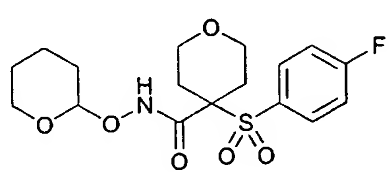
Part A: To a solution of the title compound of Example 50 (13.0 g, 24.5 mmol) in methylene chloride (100 mL) cooled to zero degrees Celsius was slowly added 50-60% m-chloroperbenzoic acid (17.1 g, 49.5 mmol). The mixture was stirred one hour at zero degrees Celsius followed by an additional 3 hours as the temperature rose to ambient conditions. Water (200 mL) was added and the mixture was neutralized with 10% ammonium hydroxide (100 mL). The organic layer was washed with water (1x-200 mL) and dried over $MgSO_4$. Concentrating *in vacuo* provided an orangish oil (3.5 g, 33%). The water/10% ammonium hydroxide solution was saturated with sodium chloride and extracted with ethyl acetate (2x-400 mL). The organic layer was dried over $MgSO_4$ and concentrated to afford the THP-protected sulfone-thiopyran-p-F as an orange foam (6.1 g, 57%).

Part B: To a solution of the THP-protected sulfone-thiopyran-p-F from A (6.0 g, 13.8 mmol) in N,N-dimethylacetamide (25 mL) was added tyramine (3.8 g, 28 mmol) followed by cesium carbonate (13.6 g, 42

mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (20 g). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected tyramine product as a tan oil (1.0 g, 13%).

Part C: To a solution of the crude THP-protected tyramine product from part B (1.0 g, 1.8 mmol) in acetonitrile (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a tan solid (0.9 g, 99%). MS (FAB) $M^{+}H$ calculated for $C_{20}H_{25}ClN_2O_7S_2$: 469, found 469.

Example 55: Preparation of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide



Part A: In dry equipment under nitrogen, sodium metal (8.97 g, 0.39 mol) was added to methanol (1000 mL) at two degrees Celsius. The reaction was stirred at ambient temperature for forty five minutes at which time the sodium had dissolved. The solution was chilled to five degrees Celsius and p-fluorothiophenol (41.55 mL, 0.39 mmol) was added,

followed by methyl 2-chloroacetate (34.2 mL, 0.39 mol). The reaction was stirred at ambient temperature for four hours, filtered, and concentrated *in vacuo* to give the sulfide as a clear colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) were added water (100 mL) and Oxone®(720 g, 1.17 mol) at 20 degrees Celsius. An exotherm to 67 degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with methanol. The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone from part B (28.5 g, 0.123 mol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 0.27 mol), bis-(2-bromoethyl)ether (19.3 mL, 0.147 mol), 4-dimethylaminopyridine (0.75 g, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. The reaction was slowly poured into 1N HCl (300 mL), the resultant solid filtered and the cake washed well with hexanes. The solid was recrystallized from ethyl acetate/hexanes to give the pyran compound as a beige solid (28.74 g, 77%). MS (ES+) MH+ calculated for $C_{13}H_{15}O_5S_1F_1$: 303, found 303.

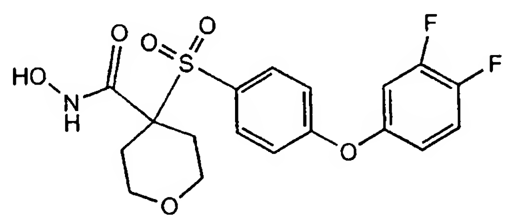
Part D: In dry equipment under nitrogen, the pyran compound from part C (8.0 g, 26.5 mmol) was

dissolved in dry tetrahydrofuran (250 mL) and a solution of potassium trimethylsilonate (10.2 g, 79.5 mmol) in dry tetrahydrofuran (15 mL) was added at ambient temperature. After ninety minutes, water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was heated in diethyl ether, the solid filtered and dried to give the carboxylic acid as a crystalline solid (5.78 g, 76%). HRMS (ES-) M-H calculated for $C_{12}H_{13}O_5\ S_1F_1$: 287.04, found 287.04.

Part E: In dry equipment under nitrogen, the carboxylic acid from part D (9.1g, 31.6 mmol) was dissolved in dry N,N-dimethylformamide (70 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (5.1 g, 37.9 mmol), N-methylmorpholine (10.4 mL, 94.8 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (11.5 g, 98 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.48 g, 44.2 mmol). After three hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the title compound as a crystalline solid (9.7 g, 80%). HRMS

(ES+) MH+ calculated for $C_{17}H_{22}NO_6S_1F_1$: 388.12, found 388.12.

Example 56: <u>Preparation of 4-[[4-(3,4-difluorophenoxy)-phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide</u>

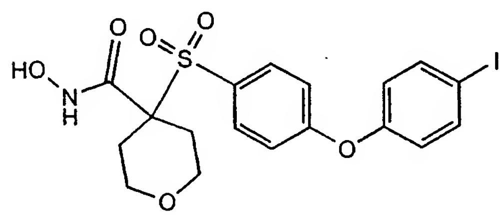


Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 3,4-difluorophenol (1.0 g, 7.7 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (8.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected difluoro product in solution.

Part B: To the collected THP-protected difluoro product from A in acetonitrile/ water (50 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white

solid (1.02 g, 48.6%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{17}FNO_6S$: 414, found 414.

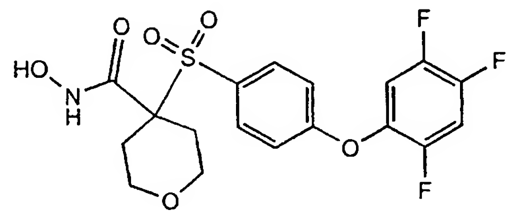
Example 57: <u>Prepartion of Tetrahydro-N-hydroxy-4-[[4-(4-iodophenoxy) phenyl]sulfonyl]-2H-pyran-4-carboxamide</u>



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 4-iodophenol (1.7 g, 7.8 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (5.7 g, quantitative) Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected iodo product in solution.

Part B: To the solution of the crude THP-protected iodo product from A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (2.6 g, 99%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{18}INO_6S$: 504, found 504.

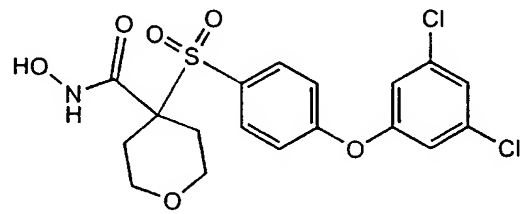
Example 58: Preparation of Tetrahydro-N-hydroxy-4-[[4-(2,4,5-trifluorophenoxy)phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide(6 mL) was added 2,4,5-trifluorophenol (1.2 g, 7.8 mmol), followed by cesium carbonate (10.1 g, 31.0 mmol). The reaction was heated at 95 degrees Celsius for thirty-two hours. Removinging the N,N-dimethylacetamide *in vacuo* afforded a brown solid (5.7 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected phenol product (1.2 g, 44%).

Part B: To the solution of the crude THP-protected phenol product from Part A (1.2 g, 2.3 mmol)in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (0.79 g, 79%). MS (FAB) M^-H calculated for $C_{18}H_{16}F_3NO_6S$: 430, found 430.

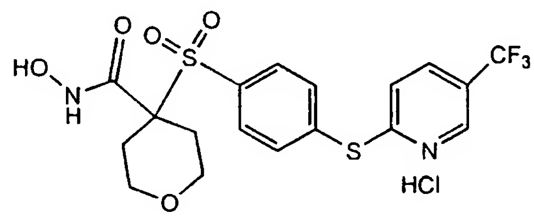
Example 59: Preparation of 4-[[4-(3,5-dichlorophenoxy)-phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 3,5-dichlorophenol (1.3 g, 7.8 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for twelve hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (5.7 g, quantitative). The residue was taken up in acetonitrile/water (20 mL) and acidified to pH=6. A white precipitate formed and was collected affording the THP-protected product as a white cake (1.8 g, 64%).

Part B: To the THP-protected product from Part A (1.8 g, 3.4 mmol)in acetonitrile/water (20 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (0.71 g, 47%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{17}Cl_2NO_6S$: 447, found 447.

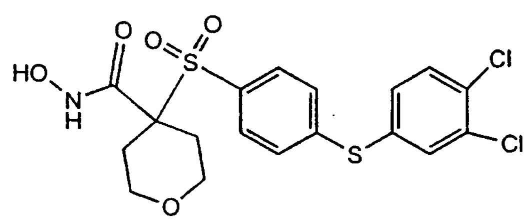
Example 59: Preparation of Tetrahydro-N-hydroxy- 4-[[4-[[5-(trifluoromethyl)-2-pyridinyl]-thio]phenyl]sulfonyl]-2H-pyran-4-carboxamide monohydrochloride



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 5-(trifluoromethyl)-2-pyridinyl thiophenol (1.4 g, 7.8 mmol), followed by potassium carbonate (2.2 g, 15.6 mmol). The reaction was heated at 65 degrees Celsius for twelve hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (5.4 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-protected product from Part A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (0.20 g, 8%). MS (FAB) M^+H calculated for $C_{18}H_{17}F_3N_2O_5S_2$: 463, found 463.

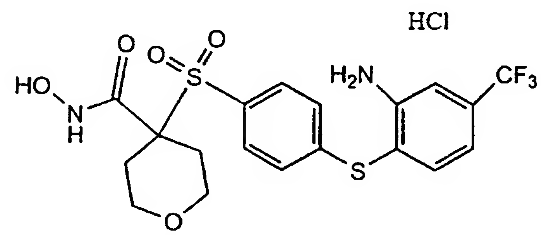
Example 60: Preparation of 4-[[4-(3,4-dichlorophenyl]-thio]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 3,4-dichlorothiophenol (1.4 g, 7.8 mmol) followed by potassium carbonate (2.2 g, 15.6 mmol). The reaction was heated at 70 degrees Celsius for six hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (5.6 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP protected product in solution.

Part B: To the solution of the THP-protected product from Part A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (1.5 g, 62%). MS (FAB) $M^{+}H$ calculated for $C_{18}H_{17}Cl_2NO_5S$: 463, found 463.

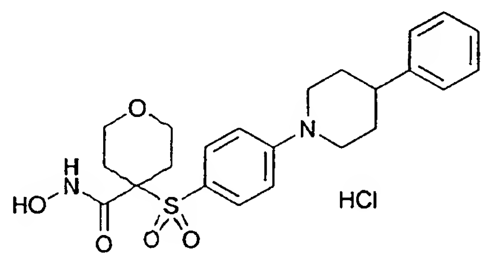
Example 61: Preparation of 4-[[4-[[2-amino-4-(trifluoromethyl)phenyl]thio]phenyl]-sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 2-amino-4-(trifluoromethyl)thiophenol hydrochloride (1.8 g, 7.8 mmol), followed by potassium carbonate (3.6 g, 26 mmol). The reaction was heated at 70 degrees Celsius for eight hours. Removing the dimethylacetamide *in vacuo* afforded a brown solid (14 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP protected product in solution.

Part B: To the solution of the THP-protected product in acetonitrile / water (40 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (1.3 g, 52%). MS (FAB) M^+H calculated for $C_{18}H_{17}Cl_2NO_6S$: 477, found 477.

Example 62: Preparation of Tetrahydro-4[[4-(4-phenyl-1-piperidinyl)phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: In dry equipment under nitrogen, sodium metal (8.97 g, 0.39 mol) was added to methanol (1000 mL) at two degrees Celsius. The reaction was stirred at ambient temperature for forty-five minutes at which time the sodium had dissolved. The solution was chilled to five degrees Celsius and p-fluorothiophenol (41.55 mL, 0.39 mmol) was added, followed by methyl 2-chloroacetate (34.2 mL, 0.39 mol). The reaction was stirred at ambient temperature for four hours, filtered, and concentrated *in vacuo* to give the sulfide as a clear colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) was added water (100 mL) and Oxone®(720 g, 1.17 mol) at 20 degrees Celsius. An exotherm to 67 degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with methanol. The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*

to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone from part B (28.5 g, 0.123 mol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 0.27 mol), bis-(2-bromoethyl)ether (19.3 mL, 0.147 mol), 4-dimethylaminopyridine (0.75 g, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. The reaction was slowly poured into 1N HCl (300 mL), the resultant solid filtered and the cake washed well with hexanes. The solid was recrystallized from ethyl acetate/hexanes to give the pyran compound as a beige solid (28.74 g, 77%). MS (ES+) MH+ calculated for $C_{13}H_{15}O_5S_1F_1$: 303, found 303.

Part D: To a solution of the pyran compound from part C (1.21 g, 4.0 mmol) in dimethyl sulfoxide (10 mL) were added cesium carbonate (3.26 g, 10 mmol) and 4-phenylpiperidine (0.64 g, 4.0 mmol) in methyl sulfoxide (10 mL). The slurry was stirred at 90 degrees Celsius for two hours. The reaction was cooled, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant solid was slurried in diethyl ether, filtered and dried to give the N-substituted piperidine as a white solid (1.2 g, 67%). MS (FAB+) MH+ calculated for $C_{24}H_{29}N_1O_5S_1$: 444, found 444.

Part E: To a slurry of the N-substituted piperidine from part D (815 mg, 1.84 mmol) in

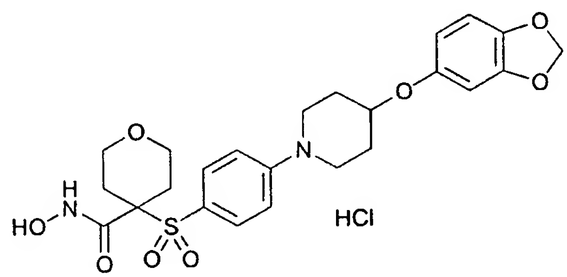
methanol (5 mL) and tetrahydrofuran (5 mL) was added 50% sodium hydroxide (3 mL). After twenty-four hours at ambient temperature, the reaction was concentrated *in vacuo*. The slurry was diluted with water (10 mL) and 6N HCl was added until the pH=7. Vacuum filtration of the resulting precipitate provided the acid as a white solid (705 mg, 89%). MS (FAB+) MH+ calculated for $C_{23}H_{27}N_1O_5S_1$: 430, found 430.

Part F: In dry equipment under nitrogen, the carboxylic acid from part E (620 mg, 1.44 mmol) was slurried in methylene chloride (10 mL) and N,N-dimethylformamide (3 mL) and the remaining reagents were added to the slurry in the following order: bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (810 mg, 1.73 mmol), N-methylmorpholine (0.5 mL, 4.34 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (190 m g, 1.59 mmol). After four hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP-protected hydroxamate as a white solid (630 mg, 83%). MS (FAB+) MH+ calculated for $C_{28}H_{22}N_2O_6\ S_1$: 529, found 529.

Part G: To a slurry of the THP-protected hydroxamate from part F (600 mg, 1.14 mmol) in dioxane (1.5 mL) was added a 4N HCl dioxane solution (1.5 mL) and methanol (1.5 mL). After two hours at ambient temperature the reaction was poured into diethyl ether (100 mL). Vacuum filtration of the

resulting precipitate provided the title compound as a light beige solid (500 mg, 91%). MS (FAB+) M+Li calculated for $C_{23}H_{28}N_2O_5S_1$: 445, found 445.

Example 63: Preparation of 4-[[4-[4-(1,3-Benzodioxol-5-yloxy)-1-piperidinyl]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride



Part A: In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below 30 degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: In dry equipment under nitrogen, the BOC piperidine from part A (5.0 g, 24.8 mmol) in dry tetrahydrofuran (100 mL) was cooled to zero

degrees Celsius and triphenylphosphine (9.77 g, 37.3 mmol) was added. After fifteen minutes of stirring at zero degrees Celsius, sesamol (5.15 g, 37.3 mmol) was added to the reaction followed by the dropwise addition of diethylazodicarboxylate (5.87 mL, 37.7 mmol). The reaction was stirred for thirty minutes at zero degrees Celsius and then at ambient temperature for twenty hours. The reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether, the triphenyl phosphine oxide filtered off and the filtrate concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (3.14 g, 39%).

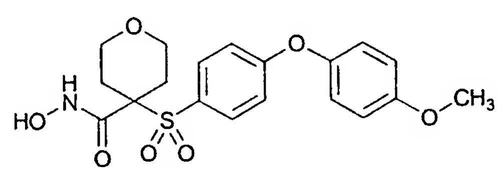
Part C: To a slurry of the substituted BOC piperidine from part B (3.14 g, 9.8 mmol) in dioxane (15 mL) was added a 4N HCl dioxane solution (15 mL). After three hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (2.3 g, 100%).

Part D: To a slurry of the hydrochloride salt from part C (0.93 g, 3.6 mmol) in N,N-dimethylformamide (10 mL) were added cesium carbonate (2.93 g, 9 mmol) and the title compound of Example 55 (1.16 g, 3.0 mmol). The slurry was stirred at 90 degrees Celsius for twenty four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered,

and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white solid (640 mg, 36%). MS (FAB+) MH+ calculated for $C_{29}H_{36}N_2O_9 S_1$: 589, found 589.

Part E: To a slurry of the THP-protected hydroxamate from part D (600 mg, 1.02 mmol) in dioxane (3 mL) were added a 4N HCl dioxane solution (3 mL) and methanol (3 mL). After one hour at ambient temperature, the reaction was poured into diethyl ether (100 mL). Vacuum filtration of the resulting precipitate provided the title compound as a light beige solid (440 mg, 80%). HRMS (ES+) MH+ calculated for $C_{24}H_{28}N_2O_8S_1$: 505.16, found 505.16.

Example 64: Preparation of Tetrahydro-N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-2H-pyran-4-carboxamide

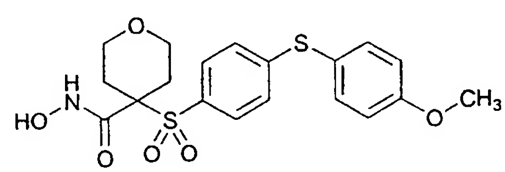


Part A: To a solution of the title compound of Example 55 (3.48 g, 9 mmol) in N,N-dimethylformamide (20 mL) were added cesium carbonate (8.8 g, 27 mmol) and p-methoxyphenol (2.23 g, 18 mmol). The slurry was stirred at 95 degrees Celsius for twenty four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate,

washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a beige foam (3.82 g, 86%). MS (FAB+) MH+ calculated for $C_{24}H_{29}N_1O_8$ S_1: 492, found 492.

Part B: To a slurry of the THP-protected hydroxamate from part A (3.6 g, 7.33 mmol) in dioxane (18 mL) were added a 4N HCl dioxane solution (18 mL) and methanol (18 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.1 g, 70%). HRMS (ES+) MH+ calculated for $C_{19}H_{21}N_1O_7S_1$: 408.11, found 408.11.

Example 65: Preparation of Tetrahydro-N-hydroxy-4-[[4-(4-methoxyphenylthio)phenyl]-sulfonyl]-2H-pyran-4-carboxamide

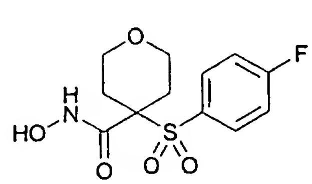


Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylformamide (20 mL) were added potassium carbonate (1.33 g, 9.6 mmol) and p-

methoxybenzenethiol (1.48 mL, 12 mmol). The slurry was stirred at 65 degrees Celsius for twenty-four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate /hexanes) provided the substituted THP-protected hydroxamate as a white foam (4.1 g, 100%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{24}H_{29}N_1O_7S_2$: 525.17, found 525.17.

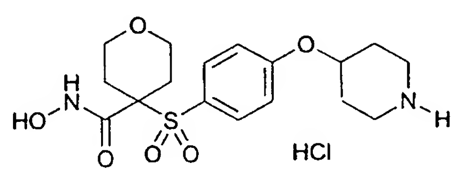
Part B: To a slurry of the THP-protected hydroxamate from part A (4.0 g, 7.9 mmol) in dioxane (20 mL) was added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.21 g, 67%). HRMS (ES+) MH+ calculated for $C_{19}H_{21}N_1O_6S_2$: 424.09, found 424.09.

Example 66: Preparation of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a slurry of the title compound of Example 55 (530 mg, 1.38 mmol) in dioxane (5 mL) was added a 4N HCl dioxane solution (5 mL) and methanol (5 mL). After fifteen minutes at ambient temperature the reaction was concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile/water) provided the title compound as a beige solid (140 mg, 34%). HRMS (ES+) M+ NH_4^+ calculated for $C_{12}H_{14}N_1O_5S_1F_1$: 321.09, found 321.09.

Example 67: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-piperidinyloxy)phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride

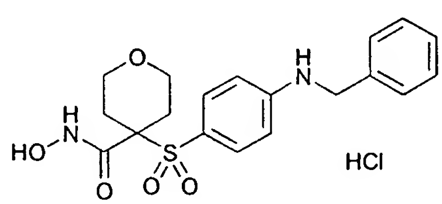


Part A: In dry equipment under nitrogen, 4-hydroxy-N-t-(butoxycarbonyl)piperidine (844 mg, 4.2 mmol) was added to 60% sodium hydride (210 mg, 5.25 mmol) in dry N,N-dimethylformamide (10 mL) at zero degrees Celsius. The slurry was stirred for two hours at ambient temperature. At five degrees Celsius, the title compound of Example 55(1.35 g, 3.5 mmol) was added and the reaction heated to 50 degrees Celsius for three hours. The reaction was cooled, quenched with water, and concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated

in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (283 mg, 14%). MS (FAB+) MH+ calculated for $C_{27}H_{40}N_2O_9S_1$: 569, found 569.

Part B: To a slurry of the THP-protected hydroxamate from part A (530 mg, 0.93 mmol) in dioxane (5 mL) were added a 4N HCl dioxane solution (5 mL) and methanol (5 mL). After fifteen minutes at ambient temperature the reaction was concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile /water buffered with 0.01%HCl) provided the title compound as a beige solid (240 mg, 62%). HRMS (ES+) MH+ calculated for $C_{17}H_{24}N_2O_6S_1$: 385.14, found 385.14.

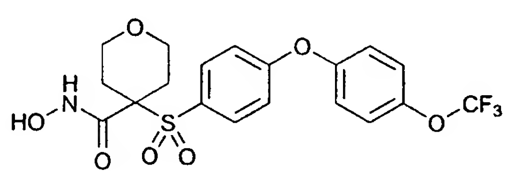
Example 68: Preparation of tetrahydro-N-hydroxy-4-[[4-[(4-phenylmethyl)amino]phenyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: In a solid phase reaction vessel, benzylamine (11.0 mL, 100 mmol) was added to Resin II (in a procedure described hereinafter; 5.0 g, 4.55 mmol) swollen in dry 1-methyl-2-pyrrolidinone (40 mL). The reaction was heated to 100 degrees Celsius

for forty-eight hours with good shaking. The resin was transferred to a frit and washed four times with N,N-dimethylformamide (30 mL), four times with methanol (30 mL), four times with methylene chloride (30 mL), and dried. The dried resin was transferred to a flask and a solution of 95% trifluoroacetic acid/5%water (50 mL) was added. The slurry was stirred for one hour, filtered and the cake was washed with methylene chloride. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate and saturated sodium bicarbonate solution was added until pH=7. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile/water buffered with 0.01%HCl) provided the title compound as a reddish solid (1.01 g, 52%). HRMS (ES+) M+ NH_4^+ calculated for $C_{19}H_{22}N_2O_5S_1$: 408.16, found 408.16.

Example 69: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-trifluoromethoxy)phenoxy)phenyl]-sulfonyl]-2H-pyran-4-carboxamide

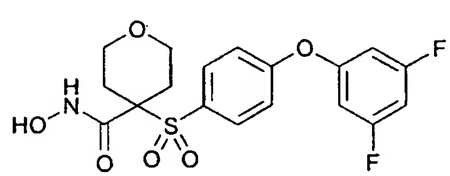


Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate

(8.8 g, 27 mmol) and p-(trifluoromethoxy)phenol (2.1 mL, 16 mmol). The slurry was stirred at 95 degrees Celsius for nineteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (4.2 g, 96%). HRMS (ES+) MH+ calculated for $C_{24}H_{26}N_1O_8S_1F_3$: 546.14, found 546.14.

Part B: To a slurry of the THP-protected hydroxamate from part A (4.0 g, 7.3 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.2 g, 65%). HRMS (ES+) M+ NH_4^+ calculated for $C_{19}H_{18}N_1O_7S_1F_3$: 479.11, found 479.11.

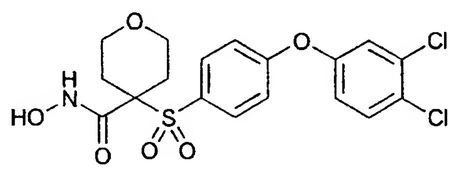
Example 70: Preparation of 4-[[4-(3,5-difluorophenoxy)phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate (8.8 g, 27 mmol) and 3,5-difluorophenol (2.1 g, 16 mmol). The slurry was stirred at 95 degrees Celsius for forty-eight hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a beige foam (3.23 g, 81%). HRMS (ES+) MH+ calculated for $C_{23}H_{25}N_1O_7\ S_1F_2$: 498.14, found 498.14.

Part B: To a slurry of the THP-protected hydroxamate from part A (3.2 g, 6.3 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the title compound as a white solid (1.5 g, 57%). HRMS (ES+) M+ NH_4^+ calculated for $C_{18}H_{17}N_1O_6\ S_1F_2$: 431.11, found 431.11.

Example 71: Preparation of 4-[[4-(3,4-dichlorophenoxy)-phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

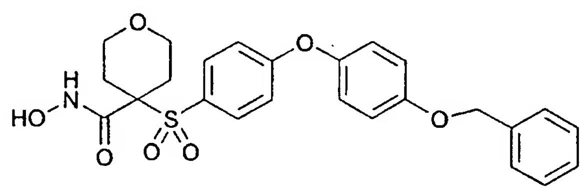


Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate (8.8 g, 27 mmol) and 3,4-dichlorophenol (2.61 g, 16 mmol). The slurry was stirred at 95 degrees Celsius for forty-one hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (4.17 g, 98%). HRMS (ES+) M+ NH_4^+ calculated for $C_{23}H_{25}N_1O_7S_1Cl_2$: 547.11, found 547.10.

Part B: To a slurry of the THP-protected hydroxamate from part A (3.5 g, 6.6 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum

filtration of the resulting precipitate provided the title compound as a white solid (2.98 g, 100%). HRMS (ES+) M+ NH_4^+ calculated for $C_{18}H_{17}N_1O_6S_1Cl_2$: 463.05, found 463.05.

Example 72: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-[(phenylmethyl)oxy]phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-carboxamide

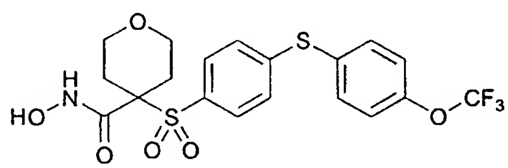


Part A: To a solution of the title compound of Example 55 (2.7 g, 7 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate (6.84 g, 21 mmol) and 4-(benzyloxy)phenol (2.8 g, 14 mmol). The slurry was stirred at 95 degrees Celsius for six hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (3.94 g, 99%). HRMS (ES+) M+ NH_4^+ calculated for $C_{30}H_{33}N_1O_8S_1$: 585.23, found 585.23.

Part B: To a slurry of the THP-protected hydroxamate from part A (1.42 g, 2.5 mmol) in dioxane (6.3 mL) were added a 4N HCl dioxane solution (6.3 mL) and methanol (6.3 mL). After fifteen minutes at

ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (0.56 g, 46%). HRMS (ES+) MH+ calculated for $C_{25}H_{25}N_1O_7\ S_1$: 484.14, found 484.14.

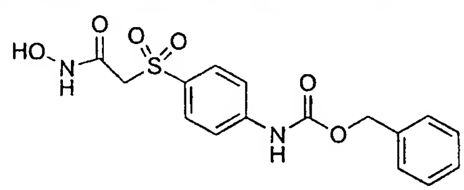
Example 73: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenylthio]-phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylformamide (20 mL) were added potassium carbonate (2.21 g, 16mmol) and p-(trifluoromethoxy)benzenethiol (2.33 g, 12 mmol). The slurry was stirred at 70 degrees Celsius for two hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white solid (4.4 g, 98%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{24}H_{26}N_1O_7S_2F_3$: 579.14, found 579.14.

Part B: To a slurry of the THP-protected hydroxamate from part A (4.15 g, 7.4 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (3.0 g, 85%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{19}H_{18}N_1O_6\ S_2F_3$: 495.09, found 495.09.

Example 74: Preparation of phenylmethyl-[4-[[2-(hydroxyamino)-2-oxoethyl]-sulfonyl]phenyl]carbamate



Part A: To a suspension of 2-(4-aminophenylthio) acetic acid (20.0 g, 0.11 mol) in methanol (100 mL), cooled to zero degrees Celsius, was slowly added thionyl chloride (24.0 mL, 0.33 mol). Additional methanol (100 mL) was added and the cooling bath was removed. The resulting mixture was heated at reflux for 2 hours. The reaction mixture was then cooled to ambient temperature and concentrated *in vacuo*. The residue was dissolved in H_2O and neutralized with saturated $NaHCO_3$. The aqueous reaction mixture was extracted with ethyl

acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the methyl ester sulfide as a dark purple oil (22.75 g, quantitative yield).

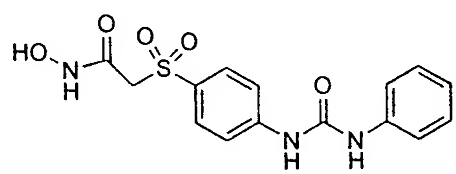
Part B: To a solution of the methyl ester sulfide of part A (10.0 g, 50.7 mmol) in dichloromethane (100 mL) was added *N*-methylmorpholine (11.2 mL, 101.4 mmol), followed by *N*-(benzyloxycarbonyloxy)succinimide (12.6 g, 50.7 mmol). The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and then washed with H_2O, 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the benzyloxy carbamate sulfide as a dark oil (16.2 g, 96%).

Part C: To a solution of the benzyloxy carbamate sulfide of part B (16.2 g, 48.7 mmol) in tetrahydrofuran (100 mL) and H_2O (10 mL) was added Oxone® (90.0 g, 146.4 mmol), and the resulting mixture was stirred at ambient temperature for 16 hours. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with H_2O, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the benzyloxy carbamate sulfone as a tan solid (15.6 g, 88%).

Part D: To a solution of the benzyloxy carbamate sulfone of part C (0.25 g, 0.69 mmol) in tetrahydrofuran (3 mL) was added 50% aqueous hydroxylamine (1.5 mL). The resulting mixture was

stirred at ambient temperature for 24 hours. The mixture was then diluted with ethyl acetate (30 mL), washed with H_2O, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* followed by washing with hot diethyl ether provided the title compound as a pale pink solid (0.20 g, 80%). MS MH^+ calculated for $C_{16}H_{17}O_6N_2S$: 365, found 365.

Example 75: Preparation of N-hydroxy-2-[[4-[[(phenylamino)carbonyl]amino]-phenyl]sulfonyl]acetamide



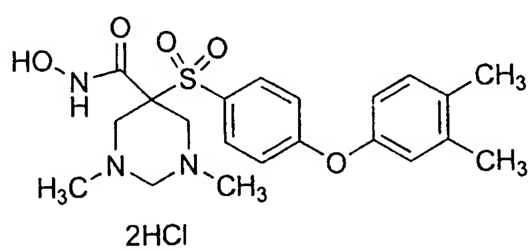
Part A: Hydrogen gas was bubbled into a suspension of the benzyloxy carbamate sulfone of part C, Example 74 (13.4 g, 36.8 mmol) and 4% Pd/C in tetrahydrofuran (100 mL). After the uptake of H_2 ceased the mixture was purged with N_2 and then filtered through a pad of Celite® washing with tetrahydrofuran. The filtrate was concentrated *in vacuo* to give the aniline as a brown solid (8.1 g, 96%).

Part B: To a suspension of the aniline of part A (0.50 g, 2.2 mmol) in dichloromethane (4 mL) was added phenyl isocyanate (0.36 mL, 3.3 mmol). The mixture was stirred at ambient temperature overnight (about 18 hours) and then diluted with

dichloromethane (50 mL). The mixture was then washed with H_2O, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the urea as a white solid (0.59 g, 78%).

Part C: To a solution of the urea of part B (0.32 g, 0.92 mmol) in tetrahydrofuran (3 mL) was added 50% aqueous hydroxylamine (1.5 mL). The resulting mixture was stirred at ambient temperature for 24 hours. The mixture was then diluted with ethyl acetate (30 mL), washed with H_2O, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo*, followed by washing with hot diethyl ether provided the title compound as a pale pink solid (0.24 g, 76%). MS MH^+ calculated for $C_{15}H_{16}O_5N_3S$: 350, found 350.

Example 78: Preparation of 5-[4-(3,4-dimethylphenoxy)phenyl]sulfonyl-N^5-hydroxy-1,3-dimethylhexahydro-5-pyrimidinecarboxamide, dihydrochloride



Part A: To a solution of part B, Example 55 (2.00 g, 8.61 mmol) and 1,3,5-trimethylhexahydro-1,3,5-triazine (1.21 mL, 8.61 mmol) in benzene (20 mL) was slowly added trifluoroacetic acid (0.66 mL,

8.61 mmol). The resulting mixture was heated at reflux for 1 hour and then cooled to ambient temperature. The mixture was then extracted with 2*N* HCl. The aqueous layer was neutralized with saturated $NaHCO_3$ and then extracted with diethyl ether. The organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the tetrahydropyrimidine as a clear oil (2.31 g, 81%).

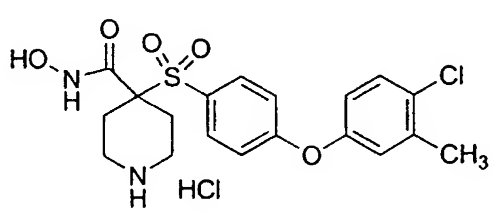
Part B: To a solution of the tetrahydopyrimidine of part A (1.26 g, 3.81 mmol) in *N,N*-dimethylformamide (5.0 mL) were added 3,4-dimethylphenol (0.559 g, 4.58 mmol) and Cs_2CO_3 (3.72 g, 11.43 mmol). The resulting mixture was heated at 90 degrees Celsius for 16 hours. After cooling to ambient temperature, the reaction was diluted with H_2O and extracted with ethyl acetate. The organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate) gave the biaryl ether as a pale amber oil (1.40 g, 85%).

Part C: To a solution of the biaryl ether of part B (0.936 g, 2.16 mmol) in tetrahydrofuran (5.0 mL) was added potassium trimethylsilanolate (0.360 g, 2.81 mmol). The resulting mixture was stirred at ambient temperature for 48 hours and then the solvent was removed. The resulting residue was dissolved in dichloromethane (5.0 mL) then, *N*-methylmorpholine (0.712 mL, 6.48 mmol) and *O*-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.278 g, 2.38 mmol) were added. After stirring at ambient temperature for 10 minutes, PyBroP® (1.21 g, 2.59

mmol) was added. The resulting mixture was stirred at ambient temperature overnight (about 18 hours), then diluted with dichloromethane (50 mL) and washed with H_2O. The organic layer was removed and washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate) provided the hydroxamate as a white solid (0.970 g, 87%).

Part F: To a suspension of the hydroxamate of part E (0.667 g, 1.29 mmol) in dioxane (3.0 mL) and methanol (1.0 mL) was added a solution of 4*N* HCl in dioxane (3.22 mL, 12.9 mmol). After stirring at ambient temperature for 30 minutes, the reaction mixture was concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile/H_2O/trifluoroacetic acid) provided the title compound as a white solid (0.379 g, 58%). MS MH^+ calculated for $C_{21}H_{28}O_5N_3S$: 434, found 434.

Example 79: Preparation of 4-[[4-(4-chloro-3-methylphenoxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a suspension of isonipectic acid (50.0 g, 0.39 mol) in methanol (300 mL) cooled to zero degrees Celsius was slowly added dropwise

thionyl chloride (85.0 mL, 1.16 mol). Once the addition was complete the cooling bath was removed and the mixture was heated at reflux for 2 hours. After cooling to ambient temperature the reaction mixture was concentrated *in vacuo*. The resulting solids were suspended in ethyl acetate and then washed with saturated $NaHCO_3$. The aqueous layer was concentrated *in vacuo* and the resulting solids were dissolved in hot ethyl acetate and decanted from the salts. The organic layers were then concentrated *in vacuo* to give the methyl ester as a white solid (55.4 g, quantitative yield).

Part B: To a solution of di-tert-butyl dicarbonate (15.3 g, 70.0 mmol) in tetrahydrofuran (100 mL) was added the methyl ester of part A (10.0 g, 70.0 mmol). The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and then concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexane) provided the Boc-piperidine methyl ester as a pale yellow oil (10.1 g, 59%).

Part C: To a solution of the Boc-piperidine methyl ester of part B (23.31 g, 0.096 mol) in tetrahydrofuran (500 mL), cooled to minus 40 degrees Celsius, was slowly added lithium diisopropylamide (57.5 mL, 2.0 *M* in THF, 0.115 mol). The resulting mixture was stirred at minus 40 degrees Celsius for 1 hour and then at zero degrees Celsius for 30 minutes. The mixture was then recooled to minus 40 degrees Celsius and a solution of the disulfide from Part A, Example 6 (24.37 g, 0.096 mol)

in tetrahydrofuran (60 mL) was slowly added. The resulting mixture was slowly warmed to ambient temperature overnight (about 18 hours) and then H_2O (200 mL) was added. The mixture was then concentrated *in vacuo* and the aqueous layer was extracted with ethyl acetate. The organic layers were washed with 0.5 *M* NaOH, H_2O, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) gave the sulfide as an amber oil (28.1 g, 79%).

Part D: To a solution of the sulfide of part C (28.2 g, 0.076 mol) in dichloromethane (250 mL), cooled to zero degrees Celsius, was added m-chloroperoxy-benzoic acid (48 g, 0.152 mol). The resulting mixture was stirred at zero degrees Celsius for 1 hour, and then at ambient temperature for 2.5 hours. The mixture was then diluted with H_2O and 10% NH_4OH. The organic layer was washed with 10% NH_4OH, H_2O and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a white solid (24.7 g, 81%).

Part E: To a solution of the sulfone of part D (3.00 g, 7.47 mmol) in *N,N*-dimethylformamide (15 mL) were added 4-chloro-3-methylphenol (1.28 g, 8.96 mmol) and Cs_2CO_3 (7.30 g, 22.42 mmol). The resulting mixture was heated at 80 degrees Celsius for 8 hours. The mixture was then concentrated *in vacuo,* and the residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography

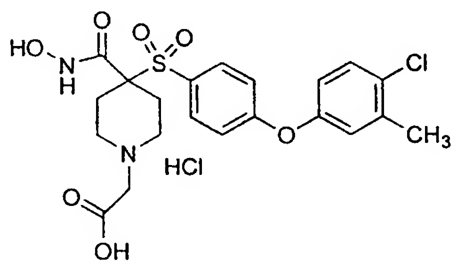
(on silica, ethyl acetate/hexane) gave the biaryl ether as a clear oil (3.26 g, 83%).

Part F: To a solution of the biaryl ether of part E (3.17 g, 6.05 mmol) in tetrahydrofuran (30 mL) was added potassium trimethylsilanolate (1.01 g, 7.87 mmol) The resulting mixture was stirred at ambient temperature for 20 hours. Additional tetrahydrofuran (40 mL) was added and the mixture was stirred at ambient temperature for 36 hours. Additional potassium trimethylsilanolate (0.233 g, 1.82 mmol) was added and the mixture was stirred at ambient temperature for 23 hours. The tetrahydrofuran was removed and the resulting residue was suspended in dichloromethane (30 mL). To the suspension was added *N*-methylmorpholine (2.00 mL, 18.15 mmol) and *O*-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.780 g, 6.66 mmol) followed by PyBroP® (3.38 g, 7.26 mmol). The mixture was stirred at ambient temperature for 24 hours and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with H_2O, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the hydroxamate as an off-white foam (2.98 g, 81%).

Part G: To a solution of the hydroxamate of part F (2.98 g, 4.89 mmol) in dioxane (14 mL) and methanol (6 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 3.5 hours, then diethyl ether (40 mL) was added and the precipitate was

collected by filtration to provide the title compound as a light pink solid (2.00 g, 88%). MS MH^+ calculated for $C_{19}H_{22}O_5N_2ClS$: 425, found 425.

Example 80: Preparation of 4-[[4-(4-chloro-3-methylphenoxy)phenyl]sulfonyl]-4-(hydroxyamino)carbonyl]-1-piperidineacetic acid, monohydrochloride

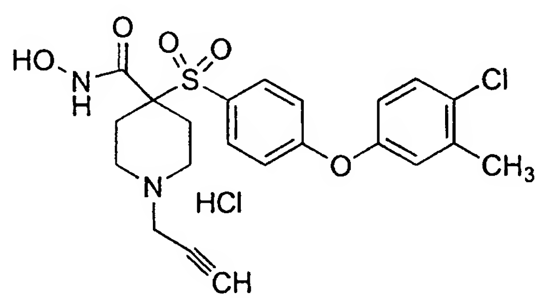


Part A: To a suspension of the title compound of Example 80 (0.250 g, 0.542 mmol) in acetonitrile (4.0 mL) were added tert-butylbromoacetate (0.088 mL, 0.542 mmol) and K_2CO_3 (0.150 g, 1.08 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, then filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was then concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile/H_2O/trifluoroacetic acid) provided the tert-butyl ester as a white solid (0.156 g, 53%).

Part B: The tert-butyl ester of part A (0.156 g, 0.289 mmol) was treated with a solution of 4*N* HCl in dioxane (1.5 mL) and the resulting mixture was stirred at ambient temperature for 3.5 hours at which time additional dioxane (2 mL) was added.

After stirring at ambient temperature for 8 hours the reaction mixture was concentrated *in vacuo*. The residue was treated again with a solution of 4*N* HCl in dioxane (1.5 mL) at ambient temperature for 4 hours. Diethyl ether was added to the reaction mixture and the precipitate was collected by filtration to give the title compound as an off-white solid (0.111 g, 74%). MS MH^+ calculated for $C_{21}H_{24}O_7N_2SCl$: 483, found 483.

Example 81: Preparation of 4-[[4-(4-chloro-3-methylphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

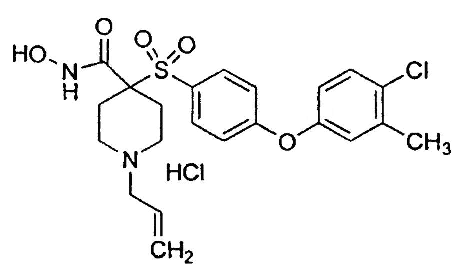


Part A: To a suspension of the title compound of Example 79 (0.500 g, 1.08 mmol) in acetonitrile (8.0 mL) were added propargyl bromide (0.126 mL, 80% solution in toluene, 1.13 mmol) and K_2CO_3 (0.300 g, 2.17 mmol). The resulting mixture was stirred at ambient temperature for 24 hours, then filtered through a pad of Celite®, washing with methanol and the filtrate was then concentrated *in vacuo*. Chromatography (on silica, ethyl acetate)

provided the *N*-propargyl hydroxamate as a tan solid (0.200 g, 40%).

Part B: To a solution of the *N*-propargyl hydroxamate of part A (0.200 g, 0.432 mmol) in acetonitrile (3.0 mL) and H_2O (0.5 mL) was added concentrated HCl (0.05 mL). The resulting mixture was stirred at ambient temperature for 5 minutes and the concentrated *in vacuo* to provide the title compound as a pink solid (0.200 g, 93%). MS MH^+ calculated for $C_{22}H_{24}O_5N_2SCl$: 463, found 463.

Example 82: Preparation of 4-[[4-(4-chloro-3-methylphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propenyl)-4-<u>piperidinecarboxamide, monohydrochloride</u>

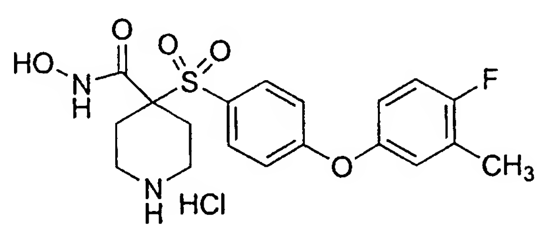


Part A: To a suspension of the title compound of Example 79 (0.500 g, 1.08 mmol) in acetonitrile (8.0 mL) were added allyl bromide (0.093 mL, 1.08 mmol) and K_2CO_3 (0.300 g, 2.17 mmol). The resulting mixture was stirred at ambient temperature for 22 hours. Additional allyl bromide (0.054 mL, 1*M* in acetonitrile, 0.054 mmol) was added and stirring was continued at ambient temperature for 6 hours. The resulting mixture was filtered through a pad of

Celite®, washing with ethyl acetate and the filtrate was concentrated *in vacuo*. Chromatography (on silica, methanol/ethyl acetate) provided the *N*-allyl hydroxamate as an off-white solid (0.080 g, 15%).

Part B: To a solution of the *N*-allyl hydroxamate of part A (0.080 g, 0.172 mmol) in acetonitrile (3.0 mL) and H_2O (1.0 mL) was added concentrated HCl (0.05 mL). The resulting mixture was stirred at ambient temperature for ten minutes and then concentrated *in vacuo* to provide the title compound as a white solid (0.100 g, quantitative yield). MS MH^+ calculated for $C_{22}H_{26}O_5N_2SCl$: 465, found 465.

Example 83: Preparation of 4-[[4-(4-fluoro-3-methylphenoxy)phenyl]sulfonyl]-N-hydroxy-4-piperidine carboxamide, monohydrochloride



Part A: To a solution of the sulfone of part D, Example 79 (5.00 g, 12.45 mmol) in tetrahydrofuran (100 mL) was added potassium trimethylsilanolate (4.79 g, 37.36 mmol). The resulting mixture was stirred at ambient temperature for 1.5 hours, diluted with H_2O and diethyl ether (100

mL). The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with H_2O. The aqueous layers were combined and acidified with 2*N* HCl (pH=2) and then extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4 to provide the acid as an off-white solid (4.61 g, 96%).

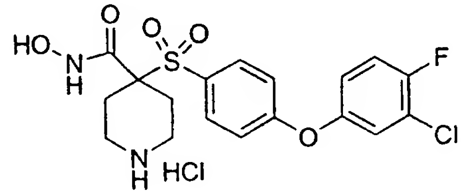
Part B: To a suspension of the acid of part A (0.830 g, 2.14 mmol) in dichloromethane (10 mL) was added *N*-methylmorpholine (0.706 mL, 6.42 mmol) and *O*-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.276 g, 2.35 mmol). After stirring at ambient temperature for 5 minutes, PyBroP® (1.20 g, 2.57 mmol) was added and the resulting mixture was stirred at ambient temperature for 19 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between H_2O and ethyl acetate. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the *p*-fluorosulfone as a white crystalline solid (0.993 g, 95%).

Part C: To a solution of the *p*-fluorosulfone of part B (0.485 g, 0.996 mmol) in *N,N*-dimethylformamide (5 mL) were added 4-fluoro-3-methylphenol (0.133 mL, 1.20 mmol) and Cs_2CO_3 (0.973 g, 2.99 mmol). The resulting mixture was heated at 60 degrees Celsius for 17 hours. Additional 4-fluoro-3-methylphenol (0.055 mL, 0.498 mmol) was added and the temperature of the reaction mixture was

increased to 80 degrees Celsius for 4 hours and then to 100 degrees Celsius for 3 hours. Additional 4-fluoro-3-methylphenol (0.133 mL, 1.20 mmol) was added and the reaction mixture was heated at 100 degrees Celsius for 7.5 hours. Additional Cs_2CO_3 was added and heating continued at 100 degrees Celsius for 17 hours. The reaction was cooled to ambient temperature and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white solid (0.490 g, 83%).

Part D: To a solution of the protected hydroxamate of part C (0.479 g, 0.808 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (2.02 mL, 8.08 mmol). The resulting mixture was stirred at ambient temperature for 1.5 hours. Diethyl ether (5 mL) was added and the precipitate was collected by filtration to give the title compound as an off-white solid (0.323 g, 90%). MS MH^+ calculated for $C_{19}H_{22}O_5N_2SF$: 409, found 409.

Example 84: Preparation of 4-[[4-(3-chloro-4-fluorophenoxy)phenyl]sulfonyl]-N-hydroxy-4-piperidine carboxamide, monohydrochloride

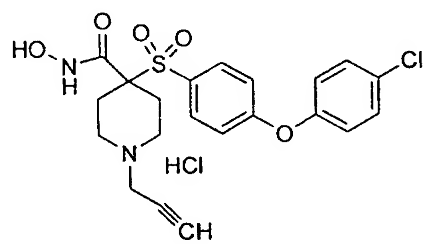


Part A: To a solution of the *p*-fluorosulfone of Part B, Example 83 (0.485 g, 0.996 mmol) in *N,N*-dimethylformamide (5.0 mL) were added 4-fluoro-3-chlorophenol (0.176 g, 1.20 mmol) and Cs_2CO_3 (0.973 g, 2.99 mmol). The resulting mixture was heated at 60 degrees Celsius for 17 hours, then additional 4-fluoro-3-chlorophenol (0.073 g, 0.498 mmol) was added and the reaction mixture was heated at 80 degrees Celsius for 24 hours then increased to 90degrees Celsius. After heating 90 degrees Celsius for 7 hours additional 4-fluoro-3-chlorophenol (0.176 g, 1.20 mmol) was added and heating was contiuned at 90 degrees Celsius for 7.5 hours. Additional Cs_2CO_3 (0.973 g, 2.99 mmol) was added and the mixture was heated at 90 degrees Celsius for 24 hours. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white solid (0.550 g, 90%).

Part B: To a solution of the protected hydroxamate of part A (0.530 g, 0.864 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (2.00 mL, 8.00 mmol).

The resulting mixture was stirred at ambient temperature for 1.5 hours. Diethyl ether (5 mL) was added and the precipitate was collected by filtration to give the title compound as an off-white solid (0.377 g, 94%). MS MH$^+$ calculated for $C_{19}H_{19}O_5N_2SFCl$: 429, found 429.

Example 85: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of sulfone of part D, Example 79 (4.53 g, 11.28 mmol) in *N,N*-dimethylformamide (20 mL) were added 4-chlorophenol (4.41 g, 13.54 mmol) and Cs_2CO_3 (11.03 g, 33.85 mmol). The resulting mixture was heated at 90 degrees Celsius for 5 hours. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the biaryl ether as a white solid (4.60 g, 78%).

Part B: To a solution of the biaryl ether of part A (4.57 g, 8.96 mmol) in dioxane (10 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 2.5 hours and then additional dioxane (10 mL) was added. After stirring at ambient temperature for 1.5 hours the mixture was concentrated *in vacuo*. The resulting solid was suspended in dioxane (20 mL) and retreated with a solution of 4*N* HCl in dioxane (10 mL). The mixture was stirred at ambient temperature for 1 hour, methanol (1 mL) was added and stirring was continued at ambient temperature. After 1 hour, the mixture was concentrated *in vacuo* to give the amine as a white solid (4.09 g, quantitative yield).

Part C: To a suspension of the amine of part B (4.00 g, 8.96 mmol) in acetonitrile (20 mL) were added propargyl bromide (1.05 mL, 80% solution in toluene, 9.41 mmol) and K_2CO_3 (2.60 g, 18.82 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, filtered through a pad of Celite®, washing with ethyl acetate, and then the filtrate was concentrated *in vacuo* to provide the *N*-propargyl amine as a sticky foam (4.14 g, quantitative yield).

Part D: To a suspension of the *N*-propargyl amine of part C (4.14 g, 8.96 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (1.26 g, 9.86 mmol). The resulting mixture was stirred at ambient temperature for 17 hours and additional tetrahydrofuran (5 mL) and potassium trimethylsilanolate (0.350 g, 2.73

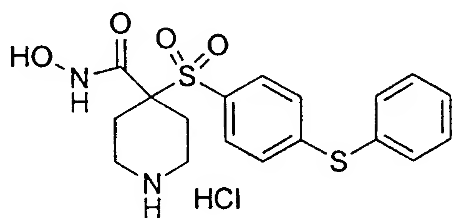
mmol) were added. After stirring at ambient temperature for 4 hours, additional tetrahydrofuran (5 mL) was added and stirring was continued at ambient temperature for 24 hours. Additional potassium trimethylsilanolate (0.115 g, 0.896 mmol) was added and the mixture was stirred at ambient temperature for 24 hours, at which time, additional potassium trimethylsilanolate was added and the resulting mixture was stirred at ambient temperature for another 24 hours. The tetrahydrofuran was removed and the residue was suspended in dichloromethane (20 mL).

To the dichloromethane suspension were added *N*-methylmorpholine (2.96 mL, 26.9 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.15 g, 9.86 mmol), followed by PyBroP® (5.01 g, 10.75 mmol). The resulting mixture was stirred at ambient temperature overnight and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white foam (3.29 g, 69%).

Part E: To a solution of the protected hydroxamate of part D (3.27 g, 6.13 mmol) in dioxane (21 mL) and methanol (7 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 4 hours and then diethyl ether (75 mL) was added. The solids were collected by filtration, washing with diethyl ether, to give the title compound as an off-white solid

(2.95 g, 99%). MS MH$^+$ calculated for $C_{21}H_{22}O_5N_2SCl$: 449, found 449.

Example 86: Preparation of 4-[[4-(phenylthio)-phenyl]-sulfonyl]-N-hydroxy-4-piperidine-carboxamide, monohydrochloride



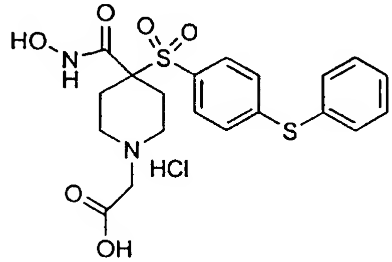
Part A: To a solution of the sulfone of part D, Example 79 (0.500 g, 1.25 mmol) in *N,N*-dimethylformamide (3.0 mL) were added thiophenol (0.154 mL, 1.50 mmol) and K_2CO_3 (0.518 g, 3.75 mmol). The resulting mixture was stirred at ambient temperature for 24 hours and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the biaryl thioether as a clear sticky oil (0.480 g, 78%).

Part B: To a solution of the biaryl thioether of part A (2.01 g, 4.09 mmol) in tetrahydrofuran (40 mL) was added potassium trimethylsilanolate (0.682 g, 5.31 mmol). The resulting mixture was stirred at ambient temperature for 23 hours and then concentrated *in vacuo*. The

residue was then suspended in dichloromethane (20 mL) then *N*-methylmorpholine (1.35 mL, 12.27 mmol) and 50% aqueous hydroxylamine (0.265 mL, 4.50 mmol) were added, followed by PyBroP® (2.29 g, 4.91 mmol). The resulting mixture was stirred at ambient temperature for 16 hours and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. A portion of the sample was subjected to reverse phase chromatography (on silica, acetonitrile/H_2O/trifluoroacetic acid) to give the hydroxamate as an off-white solid (0.190 g).

Part C: To a solution of the hydroxamate of part B (0.181 g, 0.367 mmol) in dioxane (5 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (3 mL). The resulting mixture was stirred at ambient temperature for 3 hours and then concentrated *in vacuo* to give the title compound as an off-white solid (0.170 g, quantitative yield). MS MH^+ calculated for $C_{18}H_{21}O_4N_2S_2$: 393, found 393.

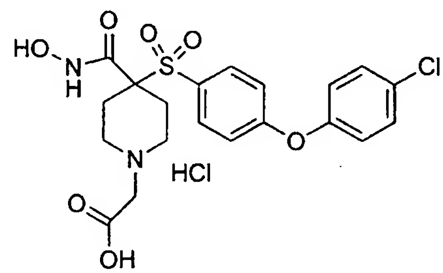
Example 87: Preparation of 4-[(hydroxyamino)-carbonyl]-4-[[4-(phenylthio)phenyl]-sulfonyl]-1-piperidineacetic acid, monohydrochloride



Part A: To a solution of the compound of Example 86 (0.322 g, 0.751 mmol) in acetonitrile (4.0 mL) were added tert-butylbromoacetate (0.121 mL, 0.751 mmol) and K_2CO_3 (0.207 g, 1.50 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, filtered through a pad of Celite®, washing with ethyl acetate, and the filtrate was concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile /H_2O/trifluoroacetic acid) provided the tert-butyl ester as an off-white solid (0.150 g, 40%).

Part B: The tert-butyl ester of part A (0.145 g, 0.286 mmol) was treated with a solution of 4*N* HCl in dioxane (3.0 mL). The resulting mixture was stirred at ambient temperature for 7 hours, diethyl ether was added and the precipitate was collected by filtration. Reverse phase chromatography (on silica, acetonitrile /H_2O/HCl) provided the title compound as an off-white solid (0.060 g, 43%). MS MH^+ calculated for $C_{20}H_{23}O_6N_2S_2$: 451, found 451.

Example 88: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-4-[(hydroxyamino)-carbonyl]-1-piperidineacetic acid, monohydrochloride



Part A: To a suspension of 4-bromopiperidine hydrobromide (40.0 g, 0.16 mol) in tetrahydrofuran (200 mL) was slowly added triethylamine (45.4 mL, 0.33 mol), followed by di-tert-butyl dicarbonate (37.4 g, 0.17 mol), which was added in several portions. The resulting mixture was stirred at ambient temperture for 17 hours then filtered and concentrated *in vacuo*. The solids were washed with hexanes and then collected by filtration to give the Boc-piperidine compound as an amber oil (45.8 g, >100%).

Part B: To a solution of 4-fluorophenol (25.0 g, 0.20 mol) in acetone (150 mL), degassed with N_2, was added Cs_2CO_3 (79.7 g, 0.25 mol). After degassing the resulting mixture with N_2 for 5 minutes, the Boc-piperidine compound of part A (43.1 g, 0.16 mol) was added. The resulting mixture was stirred at ambient temperature for 22 hours and then filtered through a pad of Celite®, washing with acetone. The

residue was washed with diethyl ether and the solids were collected by filtration to provide the sulfide as a yellow oil (47.6 g, 93%).

Part C: To a solution of the sulfide of part B (47.3 g, 0.15 mol) in dichloromethane (350 mL), cooled to zero degrees Celsius, was added m-chloroperoxy-benzoic acid (80 g, 57-86%). Additional dichloromethane (50 mL) was added and the mixture was stirred at zero degrees Celsius for 1 hour and then for 1.5 hours at ambient temperature. The reaction mixture was diluted with H_2O and aqueous sodium meta-bisulfite (4.0 g in 50 mL) was added. The mixture was concentrated *in vacuo* and then extracted with diethyl ether and ethyl acetate. The combined organic layers were washed with 10% NH_4OH, saturated NaCl and dried over Na_2SO_4. Recrystallization from ethyl acetate provided the sulfone as a white solid (18.9 g, 36%).

Part D: To a solution of the sulfone of part C (8.00 g, 23.3 mmol) in *N,N*-dimethylformamide (40 mL) were added 4-chlorophenol (3.59 g, 27.96 mmol) and K_2CO_3 (22.77 g, 69.90 mmol). The resulting mixture was heated at 60 degrees Celsius for 4 hours and then increased to 80 degrees Celsius for 7 hours. The reaction was cooled to ambient temperature and then concentrated *in vacuo*. To the residue was added H_2O (100 mL) and the solids were collected by filtration to give the biaryl ether as an off-white solid (10.5 g, 99%).

Part E: To a solution of the biaryl ether of part D (5.00 g, 11.1 mmol) in tetrahydrofuran (50

mL), cooled to zero degrees Celsius, was added lithium bis(trimethylsilyl)amide (13.3 mL, 1M in tetrahydrofuran, 13.3 mmol), at such a rate that the temperature of the reaction mixture never exceeded 2 degrees Celsius. The resulting mixture was stirred at zero degrees Celsius for 30 minutes, then dimethyl carbonate (1.40 mL, 16.6 mmol) was slowly added at such a rate that the temperature of the reaction mixture never exceeded 2 degrees Celsius. The resulting mixture was then slowly permitted to warm to ambient temperature.

After 17 hours, the reaction was recooled to zero degrees Celsius and additional lithium bis(trimethylsilyl)amide (5.50 mL, 1M in tetrahydrofuran, 5.50 mmol) was slowly added at a rate such that the temperature of the reaction never exceeded 2 degrees Celsius. After stirring for 30 minutes, dimethyl carbonate (0.048 mL, 0.570 mmol) was added and stirring was continued at zero degrees Celsius for 45 minutes. Additional lithium bis(trimethylsilyl)amide (0.500 mL, 1M in tetrahydrofuran, 0.500 mmol) was slowly added and after 1 hour additional dimethyl carbonate (0.010 mL, 0.119 mmol) was added. After stirring at zero degrees Celsius for 20 minutes, saturated NH_4Cl was added and the reaction mixture was then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Recrystallization from methanol provided the

methyl ester as a white crystalline solid (3.56 g, 63%).

Part F: To a solution of the methyl ester of part E (3.54 g, 6.94 mmol) in dioxane (18 mL) and methanol (6 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 5 hours and then concentrated *in vacuo* to provide the amine as an off-white solid (3.10 g, quantitative yield).

Part G: To a solution of the amine of part F (1.50 g, 3.36 mmol) in acetonitrile (15 mL) were added tert-butylbromoacetate (0.570 mL, 3.53 mmol) and K_2CO_3 (1.16 g, 8.40 mmol). The resulting mixture was stirred at ambient temperature for 3 hours, then filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the tert-butyl ester as a pale yellow oil (1.83 g, >100%).

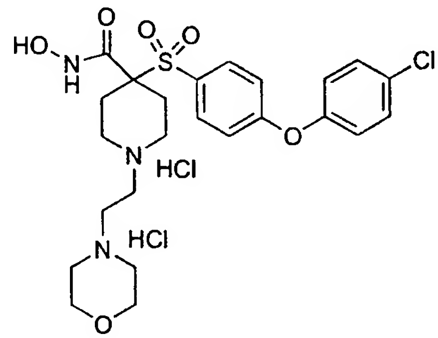
Part H: To a solution of the tert-butyl ester of part G (1.76 g, 3.36 mmol) in tetrahydrofuran (15 mL) was added potassium trimethylsilanolate (0.475 g, 3.70 mmol). The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and additional tetrahydrofuran (10 mL) was added. After stirring at ambient temperature overnight (about 18 hours), additional potassium trimethylsilanolate (0.475 g, 3.70 mmol) was added. The resulting mixture was stirred at ambient temperature for 4 hours then diluted with H_2O. The reaction mixture was acidified (pH-7) with 1*N* HCl and then concentrated *in vacuo*.

The solids were washed with diethyl ether and then with H_2O to provide the acid as an off-white solid (0.597 g, 32%).

Part I: To a suspension of the acid of part H (0.597 g, 1.17 mmol) in dichloromethane (5 mL) was added *N*-methylmorpholine (0.386 mL, 3.51 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.151 g, 1.29 mmol), followed by PyBroP® (0.655 g, 1.40 mmol). The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white foam (0.510 g, 72%).

Part J: The protected hydroxamate of part I (0.510 g, 0.837 mmol) was treated with a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 24 hours, then diethyl ether (20 mL) was added and the solids were collected by filtration to provide the title compound as a white solid (0.370 g, 87%). MS MH^+ calculated for $C_{20}H_{22}O_7N_2SCl$: 469, found 469.

Example 89: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-N-hydroxy-1-[2-(4-morpholinyl)ethyl]-4-piperidine-carboxamide, dihydrochloride



Part A: To a solution of the amine of part F, Example 88 (1.00 g, 2.24 mmol) in acetonitrile (10 mL) were added 4-(2-chloroethyl)morpholine (0.438 g, 2.35 mmol) and K_2CO_3 (1.24 g, 8.96 mmol). The resulting mixture was stirred at ambient temperature for 1.5 hours then a catalytic amount of NaI was added and stirring was continued at ambient temperature for 21 hours. The temperature of the reaction mixture was then increased to 60 degrees Celsius for 29 hours. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the ester as an oily solid (1.15 g, 98%).

Part B: To a solution of the ester of part A (1.15 g, 2.20 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.579 g, 4.51 mmol). The reaction mixture was stirred at ambient temperature for 4 hours then additional tetrahydrofuran (10 mL) was added and stirring was continued at ambient temperature overnight (about 18 hours). The reaction mixture was diluted with H_2O (10 mL) and acidified (pH-7) with 1*N* HCl. The resulting

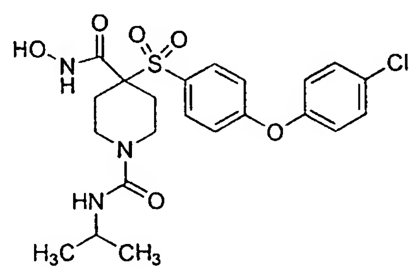
precipitate was collected by filtration to provide the acid as a gray solid (0.753 g, 72%).

Part C: To a suspension of the acid of part B (0.750 g, 1.47 mmol) in dichloromethane (7 mL) were added *N*-methylmorpholine (0.500 mL, 4.55 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.198 g, 1.62 mmol), followed by PyBroP® (0.822 g, 1.76 mmol). The resulting mixture was stirred at ambient temperature for 24 hours then additional *N*-methylmorpholine (0.242 mL, 2.21 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.052 g, 0.441 mmol) and PyBroP® (0.343 g, 0.735 mmol) were added. The resulting mixture was stirred at ambient temperature for 23 hours and then additional O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.017 g, 0.145 mmol) and PyBroP® (0.073 g, 0.157 mmol) were added. The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, methanol/chloroform) provided the protected hydroxamate as an off-white solid (0.750 g, 84%).

Part D: The protected hydroxamate of part C (0.730 g, 1.20 mmol) was treated with a solution of 4*N* HCl in dioxane (10 mL) and methanol (1 mL). The resulting mixture was stirred at ambient temperature for 1 hour, then diethyl ether (20 mL) was added and the solids were collected by filtration to provide the title compound as a pale yellow solid (0.625 g,

87%). MS MH$^+$ calculated for $C_{24}H_{31}O_6N_3SCl$: 525, found 525.

Example 90: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-N^4-hydroxy-N^1-(1-methylethyl)-1,4-piperidine dicarboxamide



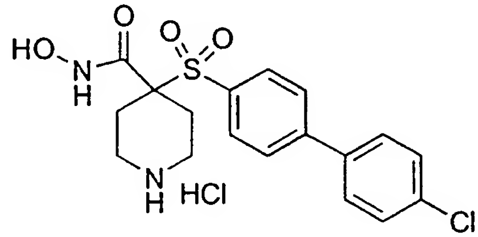
Part A: To a suspension of the amine of part F, Example 88 (0.600 g, 1.34 mmol) in dichloromethane (5 mL) were added triethylamine (0.411 mL, 2.95 mmol) and isopropyl isocyanate (0.198 mL, 2.01 mmol). The resulting mixture was stirred at ambient temperature for 2 hours then diluted with dichloromethane (50 mL). The mixture was washed with H_2O, saturated NaCl and dried over Na_2SO_4 to give the urea as an off-white solid (0.670 g, >100%).

Part B: To a solution of the urea of part A (0.640 g, 1.29 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.199 g, 1.55 mmol). The resulting mixture was stirred at ambient temperature for 17 hours at which time additional potassium trimethylsilanolate (0.015 g, 0.117 mmol) was added. The resulting mixture was stirred for an additional 24 hours then the tetrahydrofuran was

removed by blowing N_2 over the mixture. To a suspension of the residue in dichloromethane (5 mL) were added *N*-methylmorpholine (0.426 mL, 3.87 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.181 g, 1.55 mmol), followed by PyBroP® (0.902 g, 1.94 mmol). The resulting mixture was stirred at ambient temperature for 7 hours and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white solid (0.330 g, 44%).

Part C: To a solution of the protected hydroxamate of part B (0.330 g, 0.569 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 3.5 hours then diethyl ether was added. The solids were collected by filtration to give the title compound as a white solid (0.259 g, 92%). MS MH^+ calculated for $C_{22}H_{27}O_6N_3SCl$: 496, found 496.

Example 91: Preparation of 4-[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of 4-bromothiophenol (16.98 g, 89.80 mmol) in acetone (200 mL), degassed with N_2, was added K_2CO_3 (12.41 g, 89.80 mmol). After degassing the resulting mixture with N_2 for 5 minutes, the Boc-piperidine compound of part A, Example 88 (21.57 g, 81.64 mmol) was added. The resulting mixture was stirred at ambient temperature for 19 hours and then filtered through a pad of Celite®, washing with acetone. The residue was washed with diethyl ether and the solids were collected by filtration to provide the sulfide as a green oil (31.7 g, >100%).

Part B: To a solution of the sulfide of part A (31.68 g, 81.64 mmol) in dichloromethane (200 mL), cooled to zero degrees Celsius, was added m-chloroperoxybenzoic acid (56.35 g, 50-60%, 163.28 mmol). The resulting mixture became very thick, and additional dichloromethane (100 mL) was added. The mixture was stirred at zero degrees Celsius for 1.5 hours and then at ambient temperature for 1.5 hours. The reaction mixture was diluted with H_2O (300 mL) and aqueous sodium meta-bisulfte (8.00 g, 42.08 mmol in 50 mL of H_2O) was added. The dichloromethane was removed *in vacuo* and the aqueous reaction mixture was extracted with ethyl acetate. The combined organic

layers were washed with 10% NH_4OH, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfone as a yellow oil (33.42 g, >100%).

Part C: To a solution of the sulfone of part B (7.80 g, 19.34 mmol) in tetrahydrofuran (100 mL), cooled to zero degrees Celsius, was added lithium bis(trimethylsilyl)amide (23.8 mL, 1M in tetrahydrofuran, 23.8 mmol) at such a rate that the temperature of the reaction never exceeded 2 degrees Celsius. After stirring at zero degrees Celsius for 30 minutes a solution of methyl chloroformate (2.30 mL, 29.8 mmol) in tetrahydrofuran (5 mL) was added at such a rate that the temperature of the reaction never exceeded 2 degrees Celsius. The resulting mixture was then slowly allowed to warm to ambient temperature. The mixture was diluted with saturated NH_4Cl and the tetrahydrofuran was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the ester as a yellow solid (6.33 g, 69%).

Part D: To a solution of the ester of part C (4.74 g, 10.28 mmol) in dimethoxyethane (50 mL) were added 4-chlorophenylboronic acid (1.77 g, 11.30 mmol), aqueous Cs_2CO_3 (25 mL, 2.0 M, 50.0 mmol) and tetrakis(triphenylphosphine)palladium (0) (1 g). The resulting mixture was stirred at ambient temperature for 3 days. The reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate, and the filtrate was concentrated *in vacuo*.

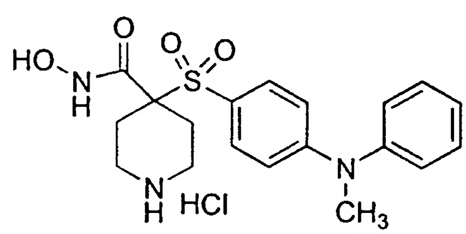
Chromatography (on silica, ethyl acetate/hexane) provided the biphenyl compound as an off-white solid (4.16 g, 82%).

Part E: To a solution of the biphenyl compound of part D (1.50 g, 3.04 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.468 g, 3.65 mmol). The resulting mixture was stirred at ambient temperature for 1 hour, additional tetrahydrofuran (5 mL) was added and the reaction mixture was stirred at ambient temperature overnight (about 18 hours). Additional tetrahydrofuran (15 mL) was added and the mixture was stirred for another 26 hours at ambient temperature. Additional potassium trimethylsilanolate (0.040 g, 0.304 mmol) was added and the mixture was stirred at ambient temperature overnight (about 18 hours) and then the solvent was removed by blowing N_2 over the reaction mixture.

To a suspension of the residue in dichloromethane (20 mL) were added added *N*-methylmorpholine (1.00 mL, 9.12 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.427 g, 3.65 mmol), followed by PyBroP® (2.13 g, 4.56 mmol). The resulting mixture was stirred at ambient temperature for 24 hours and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (1.25 g, 71%).

Part F: To a solution of the protected hydroxamate of part E (1.25 g, 2.16 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (10 mL). The resulting mixture was stirred at ambient temperature for 3.5 hours, then diethyl ether (20 mL) was added. The solids were collected by filtration to give the title compound as a white solid (0.900 g, 97%). MS MH$^+$ calculated for $C_{18}H_{20}O_4N_2SCl$: 395, found 395.

Example 92: Preparation of N-hydroxy-4-[[4-(methylphenylamino)phenyl]sulfonyl]-4-<u>piperidinecarboxamide, monohydrochloride</u>



Part A: To a solution of the ester of part C, Example 91 (1.00 g, 2.17 mmol) in toluene (4 mL) were added *N*-methylaniline (0.282 mL, 2.60 mmol), Cs_2CO_3 (0.990 g, 3.04 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.018 g, 0.02 mmol) and (R)-(+)-2,2'-bis(diphenylphosphino)1,1'-binaphthyl (BINAP; 0.021 g, 0.033 mmol). The resulting mixture was heated to 100 degrees Celsius for 20 hours. After cooling to ambient temperature, diethyl ether was added, the mixture was filtered through a pad of Celite®,

washing with diethyl ether, and the filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexane) provided the aniline as a yellow sticky gum (0.930 g, 88%).

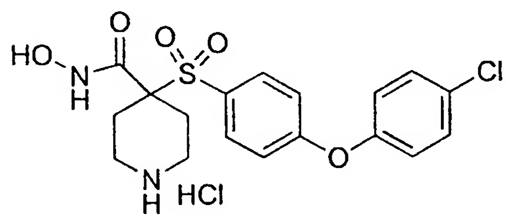
Part B: To a solution of the aniline of part A (0.930 g, 1.90 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.293 g, 2.28 mmol). The resulting mixture was stirred at ambient temperature for 19 hours and then additional potassium trimethylsilanolate (0.024 g, 0.190 mmol) was added. After stirring at ambient temperature overnight (about 18 hours) the solvent was removed by blowing N_2 over the mixture.

To a suspension of the residue in dichloromethane (10 mL) were added added *N*-methylmorpholine (0.627 mL, 5.70 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.267 g, 2.28 mmol), followed by PyBroP® (1.33 g, 2.85 mmol). The resulting mixture was stirred at ambient temperature for 2 days and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (0.860 g, 79%).

Part C: To a solution of the protected hydroxamate of part B (0.890 g, 1.55 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4*N* HCl in dioxane (5 mL). The resulting mixture was stirred at ambient temperature for 1 hour, then diethyl ether (15 mL) was added. The solids were

collected by filtration to give the title compound as a white solid (0.529 g, 80%). MS MH^+ calculated for $C_{19}H_{24}O_4N_3S$: 390, found 390.

Example 93: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a suspension of resin I (4.98 g, 5.87mmol) in 1-methyl-2-pyrrolidinone (45 mL), in a peptide flask, were added the acid of part A, Example 83 (4.55 g, 11.74 mmol), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonim hexafluorophosphate (6.11 g, 11.74 mmol) and *N*-methylmorpholine (2.58 mL, 23.48 mmol). The resulting mixture was agitated at ambient temperature for 14 hours. The resin was then collected by filtration, the filtrate was removed and set aside, and the resin was washed with *N,N*-dimethylformamide, H_2O, *N,N*-dimethylformamide, methanol, dichloromethane and finally with diethyl ether. The resin was dried *in vacuo* at ambient temperature to give the resin bound *p*-fluorosulfone as a yellow solid (6.72 g, 95%).

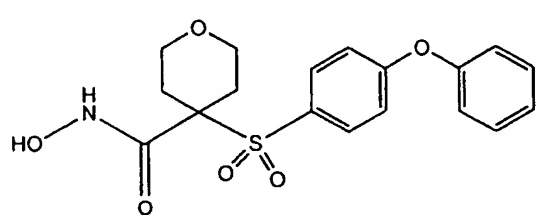
The filtrate was diluted with H_2O and extracted with ethyl acetate. The aqueous layer was acidified (pH-2.0) with 2*N* HCl and then extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The resulting residue was dissolved in 1-methyl-2-pyrrolidinone (40 mL), the above resin was added, followed by *N*-methylmorpholine (1.50 mL, 13.64 mmol) and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonim hexafluorophosphate (3.05 g, 5.86 mmol). The resulting mixture was agitated at ambient temperature for 3.5 hours. The resin was then collected by filtration and washed with *N,N*-dimethylformamide, H_2O, *N,N*-dimethylformamide, methanol, dichloromethane and finally with diethyl ether. The resin was dried *in vacuo* at ambient temperature to give the resin bound *p*-fluorosulfone as a pale orange solid (6.34 g, 89%). The loading (0.78 mmol/g) was determined by cleaving a small portion of the resin bound *p*-fluorosulfone with 95% trifluoroacetic acid/H_2O.

Part B: To a suspension of the resin bound *p*-fluorosulfone (0.700 g, 0.546 mmol) in 1-methyl-2-pyrrolidinone (3 mL) was added *p*-chlorophenol (0.702 g, 5.46 mmol) and Cs_2CO_3 (1.78 g, 5.46 mmol). The resulting mixture was heated to 110 degrees Celsius for 13 hours. The resin was then collected by filtration and washed consecutively with *N,N*-dimethylformamide, H_2O, *N,N*-dimethylformamide, 2*N* HCl, *N,N*-dimethylformamide, methanol, and dichloromethane. The resulting resin was resubjected to the above

reaction conditions for 3 hours. The resin was then collected by filtration and washed consecutively with *N,N*-dimethylformamide, H_2O, *N,N*-dimethylformamide, 2*N* HCl, *N,N*-dimethylformamide, methanol, and dichloromethane. The solid was dried *in vacuo* at ambient temperature to provide the resin bound hydroxamate as an orange solid (0.692 g, 91%).

Part C: The resin bound hydroxamate of part B (0.692 g, 0.540 mmol) was treated with 95% trifluoroacetic acid/H_2O (3 mL) for 1 hour at ambient temperature. The resin was filtered and washed with 95% trifluoroacetic acid/H_2O (3 mL) and then dichloromethane (2x 3 mL). The filtrate was then evaporated. Reverse phase chromatography (on silica, acetonitrile/H_2O/ trifluoroacetic acid) provided the hydroxamate. The resulting solid was dissolved in acetonitrile (5 mL) and H_2O (0.5 mL) and treated with concentrated HCl. The resulting mixture was stirred at ambient temperature for 5 minutes and the concentrated *in vacuo* to provide the title compound as an off-white solid (0.220 g, 91%). MS MH^+ calculated for $C_{18}H_{20}O_5N_2SCl$: 411, found 411.

Example 94: Preparation of Tetrahydro-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-2H-pyran-4-carboxamide



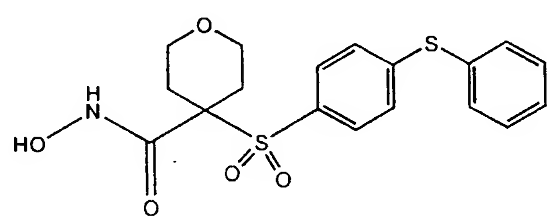
Part A: To a stirred solution of the methyl ester compound of Example 55, part C, (0.96 g, 3.2 mmol) in N,N-dimethylformamide (30 mL) was added phenol (0.3 g, 3.2 mmol), followed by cesium carbonate (3.2 g, 10 mmol). The resulting composition was heated to 70 degrees Celsius for 5 hours. The solution remained at ambient temperature for 18 hours, was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solvent was removed by rotary evaporation to yield the desired phenoxy compound (1.1 g, 92%).

Part B: Sodium hydroxide (1 g, 25 mmol) was added to a solution of the phenoxy compound of part A (1.1 g, 2.9 mmol) in THF (10 mL) and ethanol (10 mL). The resulting solution was stirred at ambient temperature for 1 hour. The solution was then heated to 80 degrees Celsius for 1 hour. The solvent was removed by rotary evaporation and the resulting sodium salt was acidified with 1 N HCl (50 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield the desired phenoxy carboxylic acid (1.1 g, 99%).

Part C: To a stirred solution of the phenoxy carboxylic acid of part B (1.1 g, 3 mmol) in DMF (7 mL) was added N-hydroxybenzotriazole-H_2O (0.623 g, 4.6 mmol), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.634 g, 3.3 mmol). After 10 minutes,

a 50% aqueous hydroxylamine solution was added (2 mL, 30 mmol) and the solution was stirred at ambient temperature for 18 hours. The solution was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with H_2O and followed by half-saturated NaCl and then dried over Na_2SO_4. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the title compound as a white solid (0.37 g, 33%). HRMS (ES^+) MH^+ for $C_{18}H_{19}NO_6S$ 378.1011. Found: 378.0994.

Example 95: Preparation of Tetrahydro-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide



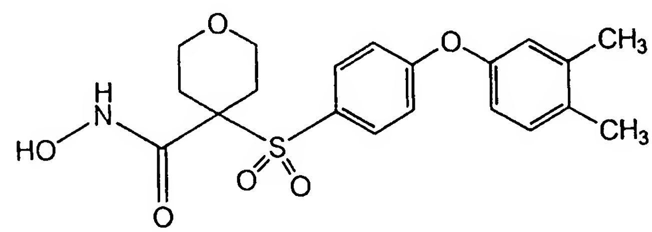
Part A: To a stirred solution under a nitrogen atmosphere of the methyl ester of Example 55, part C, (1.02 g, 3.4 mmol) in N,N-dimethylformamide (20 mL) was added thiophenol (0.37 g, 3.4 mmol), followed by cesium carbonate (3.3g, 10.1 mmol) and the solution was heated to 70 degrees Celsius for 17 hours. The solution remained at ambient temperature for 1 hour, was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over

Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the S-phenyl compound (0.6 g, 41%).

Part B: To a stirred solution of the S-phenyl compound of part A (0.6 g, 1.4 mmol) in THF (10 mL) and ethanol (10 mL) was added NaOH (0.8 g, 20 mmol). The solution was heated to 80 degrees Celsius for 1 hour. The solution remained at ambient temperature for 18 hours. The solvent was removed by rotary evaporation, the resulting sodium salt was acidified with 1 N HCl (25 mL), extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. The solvent was removed by rotary evaporation to yield the desired S-phenyl carboxylic acid (0.6 g, quantitative yield).

Part C: To a stirred solution of the S-phenyl carboxylic acid of part B (0.6 g, 1.5 mmol) in DMF (6 mL) was added N-hydroxybenzotriazole-H_2O (0.30 g, 2.2 mmol), followed by 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (0.32 g, 1.6 mmol). After 10 minutes, a 50% aqueous hydroxylamine solution was added (1.5 mL, 22 mmol) and the solution was stirred at ambient temperature 42 hours. The solution was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with H_20, followed by half-saturated NaCl and dried over sodium sulfate. Reverse phase chromatography (on silica, acetonitrile/H_20) provided the title compound as a white solid (0.15 g, 26%). HRMS (ES^+) MH^+ for $C_{18}H_{19}NO_5S_2$ 394.0783. Found: 394.0753.

Example 96: Preparation of 4-[[4-(3,4-dimethylphenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



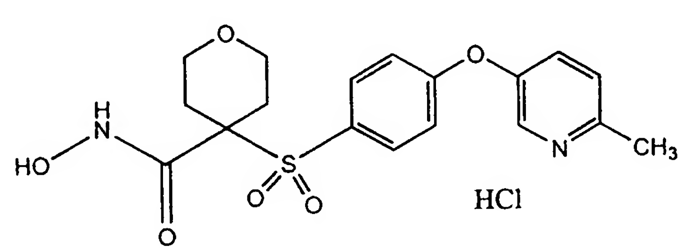
Part A: To a stirred solution of the methyl ester Example 55, part C, (1.04 g, 3.3 mmol) in N,N-dimethylformamide (30 mL) was added 3,4-dimethylphenol (0.4g, 3.3 mmol), followed by cesium carbonate (3.2 g, 10 mmol). The resulting solution was heated to 88 degrees Celsius for 5 hours. The solution was concentrated by rotary evaporation, diluted with H_2O and extracted with ethyl acetate. The organic layer dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield the desired dimethylphenoxy compound (1.2g, 91%).

Part B: To a solution of the dimethylphenoxy compound of part A (1.2 g, 3 mmol) in THF (10 mL) and ethanol (10 mL) was added NaOH (1 g, 25 mmol). The resulting solution was heated to 80 degrees Celsius for 1 hour. The solvent was removed by rotary evaporation, the resulting sodium salt was acidified with 1 N HCl (50 mL) and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The solvent was removed by rotary

evaporation to yield the desired dimethylphenoxy carboxylic acid (1.2 g, quantitative yield).

Part C: To a stirred solution of the dimethylphenoxy carboxylic acid of part B (1.2 g, 3 mmol) in DMF (7 mL) was added N-hydroxybenzotriazole-H_2O (0.623 g, 4.6 mmol), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.634 g, 3.3 mmol). After 10 minutes, a 50% aqueous hydroxylamine solution was added (2 mL, 30 mmol) and the solution was stirred at ambient temperature 18 hours. The solution was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with H_2O and followed half-saturated NaCl and dried over Na_2SO_4. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the title compound as a white solid (0.52 g, 43%). HRMS (ES^+) MH^+ for $C_{20}H_{23}NO_6S$ 406.1324. Found: 406.1302.

Example 97: Preparation of Tetrahydro-N-hydroxy-4-[[4-[(6-methyl-3-pyridinyl)oxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a stirred solution of the methyl ester of Example 55, Part C, (1.02 g, 3.4 mmol) in N,N-dimethylformamide (20 mL) was added 5-hydroxy-2-methyl-pyridine (0.54g, 5 mmol), followed by cesium carbonate (3.2g, 10 mmol). The resulting solution was heated to 70 degrees Celsius for 5 hours. The solution remained at ambient temperature for 4 days, then was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solvent was removed by rotary evaporation to yield a heavy oil from which the desired white methyl pyridine compound crystallized at ambient temperature *in vacuo* (1.2 g, 94%).

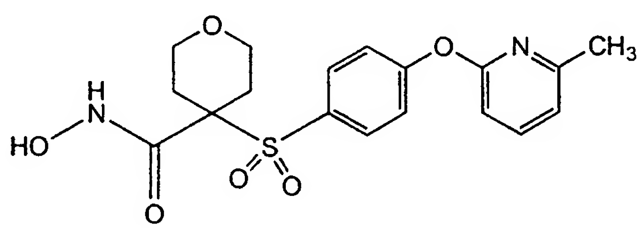
Part B: To a solution of the methyl pyridine compound of part A (1.2 g, 3.2 mmol) in THF (13 mL) was added potassium trimethylsilanoate (0.5 g, 3.5 mmol). The resulting solution was stirred at ambient temperature for 18 hours, during which time a gel formed. The solvent was removed by rotary evapotation to yield the desired methyl pyridine carboxylic acid (1.4g, quantitative yield).

Part C: To a stirred solution of the methyl pyridine carboxylic acid of part B (1.4 g, 3.2 mmol) in methylene chloride (10 mL) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (1.79 g, 3.8 mmol), followed by 4-methylmorpholine (0.97 g, 9.6 mmol), followed by O-tetrahydro-2H-pyran-yl-hydroxylamine (0.41 g, 3.5 mmol) and the solution was stirred at ambient temperature for 1.5 hours. The solution was filtered to remove a

precipitate and the solvent was removed by rotary evaporation. Chromatography (on silica, ethyl acetate/hexane) provided the O-tetrahydropyran methyl pyridine as a white solid (1.48 g, 97%).

Part D: Methanol (3 mL) was added to a stirred solution of the O-tetrahydropyran methyl pyridine of part C (1.48 g, 3.1 mmol) in 4 N HCl in dioxane (5 mL). The solution was stirred at ambient temperature for 3 hours and poured into ethyl ether. The resulting precipitate was collected by vacuum filtration. Reverse phase chromatography (on silica, acetonitrile/H_2O/HCl) provided the title compound as a white solid (0.64 g, 53%). HRMS (ES^+) MH^+ for $C_{18}H_{20}N_2O_6S$ 393.1120. Found: 393.1110.

Example 98: Preparation of Tetrahydro-N-hydroxy-4-[[4-[(6-methyl-2-pyridinyl)oxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a stirred solution of the methyl ester of Example 55, part C, (1.0 g, 3.3 mmol) in N,N-dimethylformamide (20 mL) was added 2-hydroxy-6-methyl-pyridine (0.54 g, 5 mmol), followed by cesium carbonate (3.2g, 10 mmol). The resulting solution was heated to 70 degrees Celsius for 5

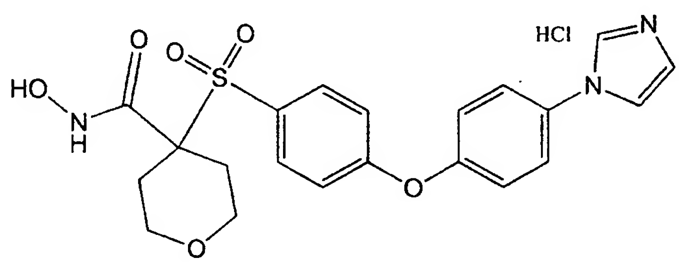
hours. The solution remained at ambient temperature for 11 hours, at which time additional 2-hydroxy-6-methyl-pyridine (0.3 g, 2.7 mmol) was added to the stirred solution and the resulting solution was heated to 70 degrees Celsius for 3 hours. The solution was concentrated by rotary evaporation, diluted with saturated NaCl in H_2O and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The solvent was removed by rotary evaporation and chromatography (on silica, ethyl acetate/methanol) provided the desired methyl pyridine as a white solid (0.63 g, 49%).

Part B: To a solution of the methyl pyridine compound of part A (0.63 g, 1.6 mmol) in THF (13 mL) was added potassium trimethylsilanoate (0.5 g, 3.5 mmol). The resulting solution was stirred at ambient temperature for 18 hours. The precipitate that formed was removed by filtration, washed with methylene chloride and dried *in vacuo* to provide the methyl pyridine carboxylic acid potassium salt (0.4 g, 55%).

Part C: To a stirred solution of the methyl pyridine carboxylic acid potassium salt of part B (0.4 g, 0.9 mmol)in N,N-dimethylformamide (5 mL) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (0.5 g, 1 mmol), followed by 4-methylmorpholine (0.27 g, 2.6 mmol), followed by a 50% aqueous hydroxylamine solution (0.6 mL, 9 mmol). The resulting solution was stirred at ambient temperature 32 hours. The solution was concentrated by rotary evaporation and reverse phase

chromatography (on silica, acetonitrile/H_2O) provided the title compound as a white solid (0.162 g, 47%). HRMS (ES^+) MH^+ for $C_{18}H_{20}N_2O_6S$ 393.1120. Found: 393.1119.

Example 99: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(1H-imidazol-1-yl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride

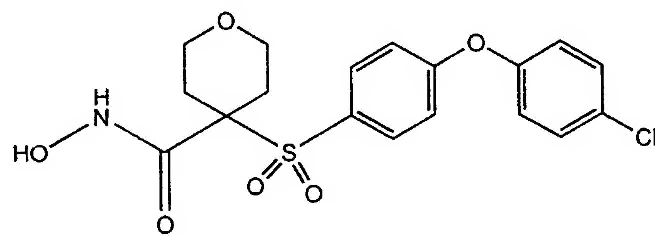


Part A: To a solution of the THP pyranfluoro compound of Example 55, part C, (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 4-(1,3-imidazole)phenol (12.9 g, 33.3 mmol), followed by cesium carbonate (32.5 g, 99.9 mmol). The reaction was heated at 65 degrees Celsius for twelve hours. Removing the dimethylacetamide *in vacuo* afforded a brown solid. Reverse phase chromatography (on silica, acetonitrile/water) gave the THP-protected product in solution.

Part B: A solution of 10% HCl_{aq} (100 mL) was slowly added to the solution of the crude THP-protected product from A in acetonitrile/water (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate

was collected, giving the title compound as a brown solid (6.0 g, 41%). MS (FAB) $M^{+}H$ calculated for $C_{218}H_{21}N_3O_6S_1$: 444, found 444.

Example 100: Preparation of 4-[[4-(4-chlorophenoxy)-phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

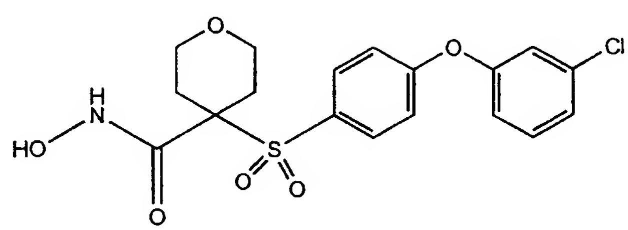


Part A: To a stirred solution of the THP pyranfluoro compound of Example 55, Part C, (2.9 g, 7.5 mmol) in N,N-dimethylformamide (15 mL) was added p-chloro-phenol (1.93 g, 15 mmol), followed by cesium carbonate (7.3 g, 22.5 mmol). The resulting composition was heated to 90 degrees Celsius for 1.5 hours. The solution remained at ambient temperature for 18 hours with stirring, and dimethylformamide (20 mL) was added to the stirred solution, followed by cesium carbonate (2 g, 6.2 mmol). The resulting composition was heated to 95 degrees Celsius for 3 hours. The solution then remained at ambient temperature 20 hours, at which time it was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solvent was removed by rotary evaporation. Chromatography (on silica,

ethyl acetate/hexane) provided the p-chloro phenoxyphenyl THP-protected hydroxamate compound (2.9 g, 78%).

Part B: To a solution of the p-chloro phenoxyphenyl THP-protected hydroxamate compound of part A (2.9 g, 5.7 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol), followed by methanol (7.5 mL). The resulting solution was stirred at ambient temperature for 1 hour. The solvent was removed by rotary evaporation. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the title compound as a white solid (1.35 g, 58%). MS (FAB) MH^+ for $C_{18}H_{18}NO_6SCl$ 412. Found: 412.

Example 101: Preparation of 4-[[4-(3-chlorophenoxy)-phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

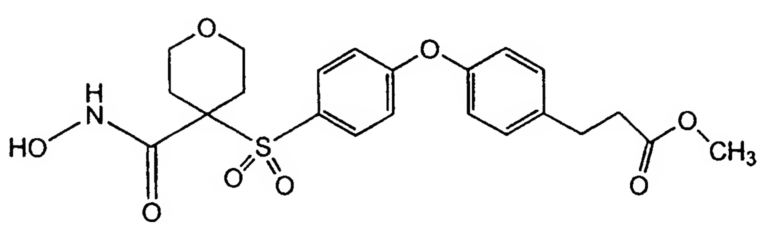


Part A: To a stirred solution of the THP pyranfluoro compound of Example 55, Part C, (5.0 g, 13 mmol) in N,N-dimethylformamide (20 mL) was added p-chloro-phenol (5 g, 39 mmol), followed by cesium carbonate (17 g, 52 mmol). The resulting solution was heated to 95 degrees Celsius for 7 hours. The solution was maintained at ambient temperature for 7

hours, diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solution was concentrated by rotary evaporation. Chromatography (on silica, ethyl acetate/hexane) provided the m-chloro phenoxyphenyl THP-protected hydroxamate compound (5.2 g, 82%).

Part B: To a solution of the m-chloro phenoxyphenyl THP-protected hydroxamate compound of part A (5.2 g, 10 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol), followed by methanol (10 mL). The resulting solution was stirred at ambient temperature for 1 hour. The solvent was removed by rotary evaporation to provide the title compound as a white solid (3.4 g, 79%). HRMS (ES^+) M + NH_4^+ for $C_{18}H_{18}NO_6SCl$ 429.0887. Found: 429.0880.

Example 102: Preparation of methyl 4-[4-[(tetrahydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]-phenoxy]benzenepropanoate

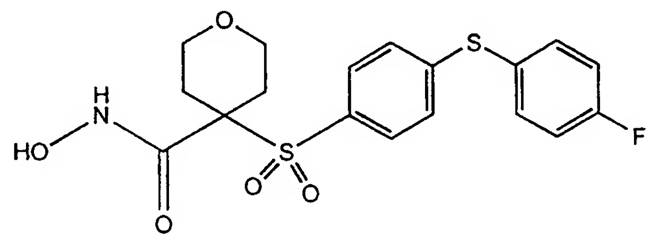


Part A: To a stirred solution of the THP pyranfluoro compound of Example 55, part C, (5.0 g, 13 mmol) in N,N-dimethylformamide (45 mL) was added

methyl 3-(4-hydroxyphenyl)-propanoate (7 g, 39 mmol), followed by cesium carbonate (17 g, 52 mmol). The resulting composition was heated to 95 degrees Celsius for 7 hours. The solution then remained at ambient temperature for 7 hours. The solution was thereafter diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solution was concentrated by rotary evaporation. Chromatography (on silica, ethyl acetate/hexane) provided the methyl propanoate phenoxyphenyl THP-protected hydroxamate compound (5.6 g, 79%).

Part B: To a solution of the methyl propanoate phenoxyphenyl THP-protected hydroxamate compound of part A (5.6 g, 10 mmol) in methanol (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol). The resulting solution was stirred at ambient temperature for 0.5 hours. The solvent was removed by rotary evaporation. The residue was dissolved in methylene chloride/ethyl acetate and the compound precipitated with hexane. The precipitate was washed with hexane and dried *in vacuo* to provide the title compound as a white solid (3.8 g, 80%). HRMS (ES^+) M^+ for $C_{22}H_{25}NO_8S$ 464.138. Found: 464.135.

Example 103: Preparation of 4-[[4-[(4-fluorophenyl)-thio]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

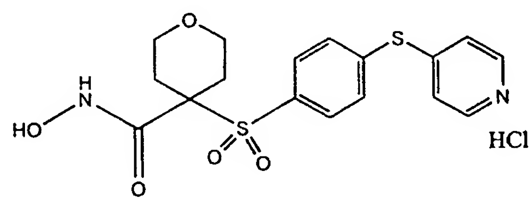


Part A: To a stirred solution under a nitrogen atmosphere of the THP pyranfluoro compound of Example 55, part C, (2.9 g, 7.5 mmol) in N,N-dimethylformamide (25 mL) was added cesium carbonate (4.9 g, 15 mmol), followed by 4-fluoro-thiophenol (1.9 g, 15 mmol). The resulting composition was heated to 95 degrees Celsius for 7 hours. Cesium carbonate was added (1.2 g, 3.8 mmol) after 1 hour of heating and again at two hours. The solution remained at ambient temperature for 9 hours, was concentrated by rotary evaporation, diluted with H_2O containing 30% brine and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over sodium sulfate. The solution was concentrated by rotary evaporation. Chromatography (on silica, ethyl acetate/hexane) followed by reverse phase chromatography (acetonitrile/H_20) provided the p-fluoro-phenyl-S-phenyl THP-protected hydroxamate compound (1.9 g, 55%).

Part B: To a solution of the p-fluoro-phenyl-S-phenyl THP-protected hydroxamate compound of part A (1.9 g, 4 mmol) in methanol (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol. The resulting solution was stirred at ambient temperature for 0.5

hours. The solvent was removed by rotary evaporation, the residue was dissolved in methylene chloride and precipitated with hexane. The precipitate was and dried *in vacuo* to provide the title compound as a white solid (1.5 g, 89%). HRMS (ES^+) $M+NH_4^+$ for $C_{18}H_{18}NO_5S_2F$ 429.0954. Found: 429.0948.

Example 104: Preparation of Tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride

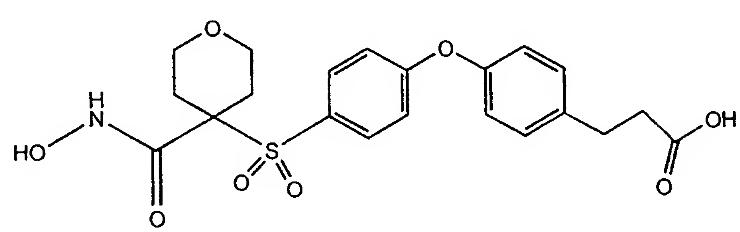


Part A: To a stirred solution of the THP pyranfluoro compound of Example 55, Part C, (2.9 g, 7.5 mmol) in N,N-dimethylformamide (20 mL) was added potassium carbonate (2.6 g, 19 mmol), followed by 4-mercaptopyridine (1.7 g, 15 mmol). The resulting composition was heated to 75 degrees Celsius for 5 hours. Potassium carbonate was added (0.26 g, 1.9 mmol) after 1 hour of heating and again at two hours. The solution remained at ambient temperature for 14 hours. The solution was concentrated by rotary evaporation, diluted with H_2O containing 30% brine and extracted with ethyl acetate. The organic layer was washed with half-saturated NaCl and dried over Na_2SO_4. The solution was concentrated by rotary evaporation.

Chromatography (on silica, ethyl acetate/hexane) provided the mercaptopyridine THP-protected hydroxamate compound (1.2 g, 33%).

Part B: To a solution of the mercaptopyridine THP-protected hydroxamate compound of part A (1.2 g, 2.5 mmol) in acetonitrile (20 mL) was added 12.5 N HCl (0.4 mL, 5 mmol), followed by methanol (3 mL). The resulting solution was stirred at ambient temperature for 1 hour. The precipitate was filtered, washed with methanol followed by ethyl ether and dried *in vacuo* to provide the title compound as a white solid (0.92 g, 86%). HRMS (ES^+) $M+NH_4^+$ for $C_{17}H_{18}N_2O_5S_2$ 395.0735. Found: 395.0734.

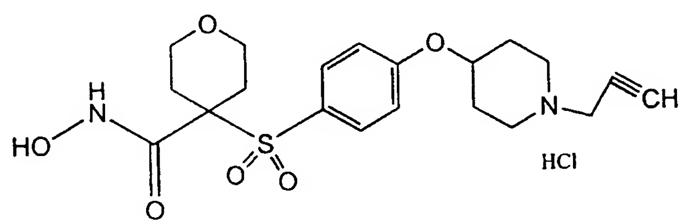
Example 105: Preparation of 4-[4-[[tetrahydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]phenoxy] benzenepropanoic acid



Part A: To a stirred solution of the title compound of Example 102 (0.1 g, 0.2 mmol) in methanol (0.5 mL) was added aqueous 1 M $Li(OH)_2$ (0.43 mL, 0.43 mmol). After standing at ambient temperature 24 hours, the solution was refluxed 20 hours. The solution was lyophilized to dryness and reverse phase

chromatography provided the title compound as a white solid (9 mg, 9%). MS (FAB) M+Li$^+$ for $C_{21}H_{23}NO_8S$ 456. Found: 456.

Example 106: Preparation of Tetrahydro-N-hydroxy-4-[[4-[[1-(2-propynyl)-4-piperidinyl]-oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a heat dried three-neck flask under a nitrogen atmosphere was added NaH (1.59g of 60%, 40 mmol) slurried in N,N-dimethylformamide (50 mL). The slurry was chilled to zero degrees Celsius using an ice bath and N-Boc-4-hydroxy piperidine was added (8 g, 40 mmol) followed by a N,N-dimethylformamide rinse (10 mL). The ice bath was removed and the stirred solution permitted to reach ambient temperature over two hours. The stirred solution was again chilled to zero degrees Celsius and the methyl ester compound of Example 55, part C, (10 g, 33 mmol) dissolved in N,N-dimethylformamide (40 mL) was added. The ice bath was removed and the solution stirred at ambient temperature 48 hours. The solution was concentrated by rotary evaporation. The solution was diluted with H_2O and extracted with

ethyl acetate. The organic layer was dried over sodium sulfate. After chromatography (on silica, ethyl acetate/hexane/methanol), the crude N-Boc methyl ester was treated with 1 N HCl in methanol. The solvent was removed by rotary evaporation. The residue was then dissolved in acetonitrile (21 mL) to which H_2O was added (21 mLs). Reverse phase chromaatography (on silica, acetonitrile/H_2O) afforded the purified piperidine methyl ester as the HCl salt (4.9g, 35%).

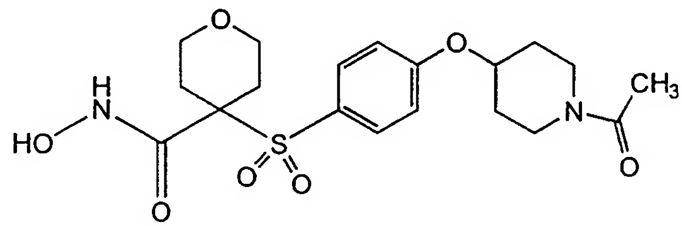
Part B: To a stirred suspension of the piperidine methyl ester HCl salt of part A (1.8 g, 4 mmol) in acetonitrile (24 mL) and was added potassium carbonate (1.8 g, 13 mmol), followed by propargyl bromide (0.58 mL of 80% solution, 5.2 mmol). The mixture was stirred at ambient temperature for 18 hours. The solution was concentrated by rotary evaporation, diluted with H_2O and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation. Chromatography (on silica, methylene chloride/methanol) provided the propargyl piperidine methyl ester compound (1.1 g, 63%).

Part C: To a solution of the propargyl piperidine methyl ester compound of part B (1.1 g,2.7 mmol) in THF (3 mL) was added potassium trimethylsilanoate (0.57 g, 4 mmol). After 5 minutes, THF was added (12 mL), followed by a second addition of THF (15 mL) after 10 more minutes. The resulting solution was stirred at ambient temperature for 18 hours, during which a gel formed. The solvent

was removed by rotary evaporation, and the residue was diluted with H_2O and washed with ethyl acetate. The aqueous layer was acidified and chromatographed (on silica, acetonitrile/H_2O) to provide the desired propargyl piperidine carboxylic acid after lyophilization (0.64 g, 59%).

Part D: To a stirred solution of propargyl piperidine carboxylic acid of part C (0.64 g, 1.6 mmol) in N,N-dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (0.3 g, 2.3 mmol), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.33 g, 1.7 mmol), followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.57 g, 4.8 mmol). The solution was stirred at ambient temperature 42 hours, concentrated by rotary evaporation, diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, followed by brine and dried over Na_2SO_4. The solution was concentrated by rotary evaporation and chromatographed on reverse phase (on silica, acetonitrile/H_2O) to provide the title compound as a white solid upon lyophilization (0.2 g, 30%). HRMS (ES^+) MH^+ for $C_{20}H_{26}N_2O_6S$ 423.159. Found: 423.159.

Example 107: Preparation of 4-[[4-[(1-acetyl-4-piperidinyl)oxy]phenyl]-sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



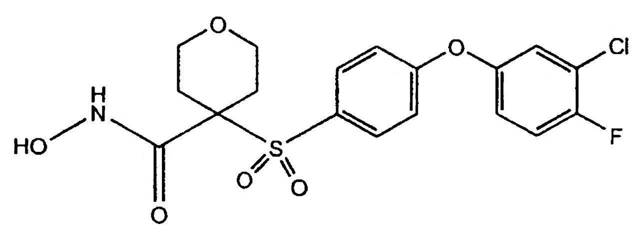
Part A: Acetic anhydride (1.7 g, 16 mmol) was added to a stirred suspension of the piperidine methyl ester HCl salt of Example 106, part A, (1.8 g, 4 mmol) in pyridine (2 mL). The mixture was stirred at ambient temperature for 20 minutes. The solution was concentrated by rotary evaporation and chromatographed (on silica, ethyl acetate/methanol) to provide the acetyl piperidine methyl ester compound (1.5 g, 83%).

Part B: To a solution of the acetyl piperidine methyl ester compound of part A (1.5 g, 3.3 mmol) in THF (5 mL) was added potassium trimethylsilanoate (0.86 g, 6 mmol). After 5 minutes, THF was added (15 mL), followed by a second addition of THF (15 mL) after 10 more minutes. The resulting solution was stirred at ambient temperature for 18 hours. The precipitate was isolated by filtration to provide the desired acetyl piperidine carboxylic acid (1.5 g, 98).

Part C: To a stirred solution of acetyl piperidine carboxylic acid of part B (0.9 g, 2 mmol) in dimethylacetamide (5 mL) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (1 g, 2.3 mmol), followed by 4-methylmorpholine (0.6 g, 6 mmol), followed by aqueous O-tetrahydro-2H-pyran-2-

yl-hydroxylamine (1.5 mL, 23 mmol) and the solution was stirred at ambient temperature 48 hours. Reverse-phase chromatography (on silica, H_2O/acetonitrile) provided title compound as a white solid (0.1 g, 12%). MS (FAB) MH^+ for $C_{19}H_{26}N_2O_7S$ 427. Found: 427.

Example 108: Preparation of 4-[[4-(3-chloro-4-fluorophenoxy)phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

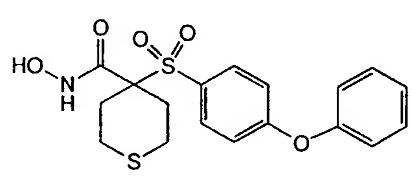


Part A: To a stirred solution of the THP pyranfluoro compound of Example 55, part C, (3.2 g, 7.7 mmol) in N,N-dimethylacetamide (15 mL) was added the 3-chloro-4-fluorophenol (1.7 mL, 12 mmol), followed by cesium carbonate (5 g, 15.5 mmol). The reaction was heated at 95 degrees Celsius for 2 hours. Cesium carbonate (2.5 g, 8 mmol) was added, and the reaction was heated at 95 degrees Celsius for 6 hours. The solution remained at ambient temperature for 8 hours. The crude reaction was then filtered to remove the cesium chloride and precipitated product. The filter cake was suspended in H_2O and acidified with HCl to pH=6. After foaming

ceased, the precipitate was removed by filtration, washed with H_2O, dissolved in H_2O/acetonitrile and chromatographed over a reverse phase HPLC column (H_2O/acetonitrile) to give the 3-chloro-4-fluoro phenoxy THP-protected hydroxamate (1.4 g, 35%).

Part B: To a stirred solution of the 3-chloro-4-fluoro phenoxy THP-protected hydroxamate from part A (1.4 g, 2.7 mmol) in acetonitrile (10 mL) was added 1N aqueous HCl (10 mL). The solution was stirred at ambient temperature for 1 hour. The acetonitrile was evaporated off at ambient temperature under a steady stream of nitrogen until a heavy precipitate formed. The precipitate was filtered and the cake was washed with H_2O followed by diethyl ether and dried under vacuum, giving the title compound as a white solid (12.5g, 96%). The compound was recrystallized from acetone/hexane, giving white crystals (10.9 g, 86%). HRMS (ES) $M+NH_4^+$ for $C_{18}H_{19}NO_6SFCl$ 447.079. Found: 447.080.

Example 109: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-phenoxy)phenyl] sulfonyl 2H-thiopyran-4-carboxamide

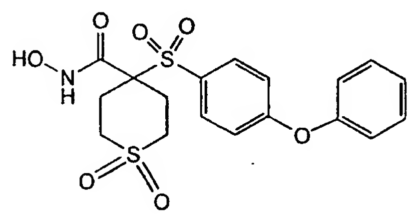


Part A: To a solution of the methylester thiopyran compound of Part C, Example 50 (MW 318, 3

g, 1.0 equivalents) in N,N-dimethylacetamide (DMA; 40 mL) were added cesium carbonate (12g, 1.5 equivalents) and phenol (1.5g). The mixture was heated to 95 degrees Celsius for 6 hours. After the reaction was cooled to ambient temperature, the reaction mixture was filtered and the N,N-dimethylacetamide was then removed via rotary evaporation. The residue was dissolved in 10% aqueous HCl (100mL) and extracted with ethyl acetate (2x). The ethyl acetate extract was dried over sodium sulfate and removed under reduced pressure to give an oil. The oil was purified on silica gel to give 2 g of methyl ester. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Part B: To a solution of the methyl ester compound of Part A (MW 392, 2 g) in THF (20 mL) was added potassium trimethylsilanoate (MW 128,1.6 g, 1.2 equivalents). The mixture stirred 2-3 hours at ambient temperature until a solid precipitate developed. After the hydrolysis was complete, N-methylmorpholine (2 mL) was added followed by PyBrop (2.3 g, 1.2 equivalents). The solution was stirred for 10 minutes, then aqueous hydroxylamine was added and stirring for an additional 2 hours. After complete reaction (2 hours) the solvent was removed via rotary evaporation. The residue was dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 1 g the title compound as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{19}NO_5S_2$: 393, found 393.

Example 110: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-phenoxy)phenyl] sulfonyl 2H-sulfonyl pyran-4-carboxamide

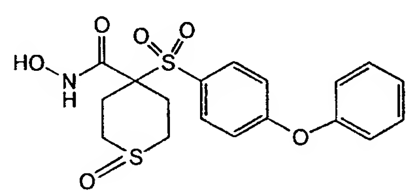


Part A: Water (50mL) was added to a solution of the compound of Example 109, part A, (2 g) in tetrahydrofuran (50mL). To this vigorously stirred mixture was added Oxone® (8 g, 3 equivalents). The course of the reaction was monitored by RPHPLC. After 3 hours, water was added and the product was extracted with ethyl acetate (100 mL, 2x). The ethyl acetate was dried over sodium sulfate. After solvent was removed via reduced pressure, 1.8 g of the phenoxy methyl ester compound was obtained as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Part B: To a solution of the phenoxy methyl ester compound of part A (MW 590, 2 g) in tetrahydrofuran (20 mL) was added potassium trimethylsilanoate (MW 128,1.2 g, 1.2 equivalents). The mixture was stirred 2-3 hours until a solid precipitate developed. After the hydrolysis was complete, N-methylmorpholine (2mL) was added followed by PyBrop (2.3 g, 1.2 equivalents). The solution was stirred for 10 minutes then aqueous hydroxylamine was

added and with stirring for an additional 2 hours. After complete reaction, (2 hours) the solvent was removed via rotary evaporation. The residue was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 500 mg of the title compound as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{19}NO_7S_2$: 425, found 425.

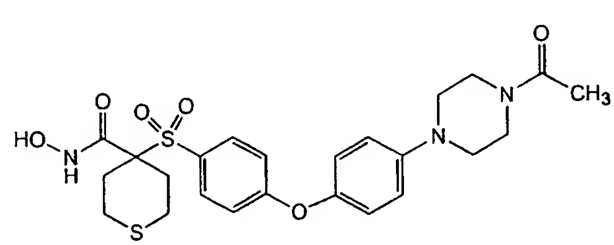
Example 111: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-phenoxy)phenyl] sulfonyl 2H-sulfoxyl pyran-4-carboxamide



Part A: To a solution of methyl ester of Example 109, part A, (2 g) in acetic acid/water (25/5mL) was added hydrogen peroxide(2mL, 30% solution). The course of this vigorously stirred solution was monitored by RPHPLC. After 3 hours, water was added and the product was extracted with ethyl acetate (100 mL, 2x). The ethyl acetate was dried over sodium sulfate. After solvent was removed via reduced pressure, 2.1 grams of the methylester sulfoxidepyran Phenyl-O-phenyl compound was obtained as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Part B: To a solution of the methylester sulfoxidepyran Phenyl-O-phenyl compound of Part A (MW 578, 1.8 g) in tetrahydrofuran (25 mL) was added potassium trimethylsilanoate (MW 128,1.2 g, 1.2 equivalents). The mixture was stirred 2-3 hours until a solid precipitate developed. After the hydrolysis was complete, N-methyl morpholine (2 mL) was added followed by PyBrop (2.3 g, 1.2 equivalents). The solution was stirred for 10 minutes then aqueous hydroxylamine was added, with stirring for an additional 2 hours. After complete reaction (12 hours) the solvent was removed via rotary evaporation. The residue was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 500 milligrams of the title compound as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{19}NO_6S_2$: 409, found 409.

Example 112: Preparation of tetrahydro-N-hydroxy-4-[[4-(1-acetyl-4-(4-piperazine-phenoxy)phenyl] sulfonyl 2H-thiopyran-4-carboxamide

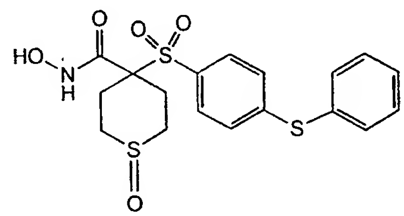


Part A: To a solution of the methylester thiopyran compound of Example 50, part C, (MW 318, 5 g, 1.0 equivalents) in N,N-dimethylacetaminde (70mL) were added cesium carbonate (MW 5.5g, 1.5 equivalents), tetrabutylammonium fluoride (2 mL, 2 M in THF) and 1-acetyl-4-(4-hydroxyphenyl)piperazine (4.9 g). The mixture was stirred and heated at 90 degrees Celsius for 6 hours. The reaction mixture was filtered and the N,N-dimethylacetamide was then removed via rotary evaporation. The residue was dissolved in water (100mL) and extracted with ethyl acetate (2x). The ethyl acetate was dried over sodium sulfate and removed under reduced pressure to give an oil. The oil was purified on silica gel to give 3 g of methyl ester. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: To a solution of the methyl ester compound of Part A (MW 433, 3 g) in tetrahydrofuran (50 mL) was added potassium trimethylsilanoate (MW 128, 0.9 g, 1.2 equivalents). The mixture was stirred 2-3 hours until a solid precipitate developed. After the hydrolysis was complete N-methyl morpholine (2 mL) was added followed by PyBrop (3.5 g, 1.2 equivalents). The solution was stirred for 10 minutes then aqueous hydroxylamine was added with stirring for an additional 2 hours. After complete reaction (2 hours) the solvent was removed via rotary evaporation. The residue was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 1.2 g of the title compound as a white solid. The ^{1}H NMR,

MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{24}H_{29}N_3O_6S_2$: 519, found 519.

Example 113: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-thiophenoxy)phenyl] sulfonyl 2H-thiopyran-4-carboxamide



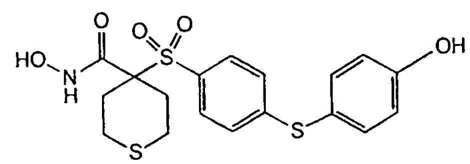
Part A: To a solution of the methylester thiopyran compound of Example 50, part C, (5 g.) in acetic acid (40mL) was added water/hydrogen peroxide(8 mL,4 mL/4 mL, 30% solution). The course of this vigorously stirred solution was monitored by RPHPLC. After 3 hours at ambient temperature, water was added and the product was extracted with ethyl acetate (100 mL, 2x). The ethyl acetate was dried over sodium sulfate. After solvent was removed via reduced pressure 4.5 g of the methylester sulfoxidepyran Ph-p-F was obtained as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Part B: To a solution of the methylester sulfoxidepyran Ph-p-F of Part A (MW 318, 5 g, 1.0 equivalents) in DMA (70 mL) were added cesium carbonate (MW 4.5g, 1.1 equivalents) and thiophenol

(1.5 g, 1.05 equivalents). The mixture was stirred 2 hours at room temperature. The reaction mixture was filtered and the N,N-dimethylacetamide was then removed via rotary evaporation. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (2x). The ethyl acetate was dried over sodium sulfate and removed under reduced pressure to give an oil. The oil was purified on prep RPHPLC to give 2 g of methyl ester sulfoxidepyran Phenyl-S-Ph compound. The ^{1}H NMR, MS, and HPLC were consistent with thedesired compound.

Part C: To a solution of the methylester sulfoxidepyran Phenyl-S-Ph of Part B (MW 590, 5 g) in tetrahydrofuran (100 mL) was added potassium trimethylsilanoate (MW 128,1.5 g, 2 equivalents). The mixture was stirred 2-3 hours at ambient temperature until a solid precipitate developed. After the hydrolysis was complete, N-methyl morpholine (6 mL) was added followed by PyBrop (4 g, 1.1 equivalents). The solution was stirred for 10 minutes then aqueous hydroxylamine was added with stirring for an additional 2 hours. After complete reaction (12 hours), the solvent was removed via rotary evaporation. The residue was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 1.9 g of the title compound as a white solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{19}NO_5S_3$: 425, found 425.

Example 114: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(4-hydroxyphenyl)thiophenoxy)-phenyl] sulfonyl 2H-thiopyran-4-carboxamide

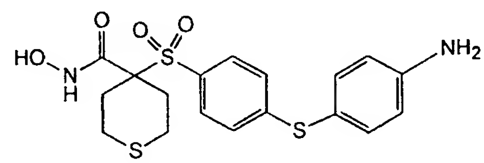


Part A: To a solution of the title compound of Example 50 (MW 402, 5 g, 1.0 equivalent) in N,N-dimethylacetamide (70 mL) was added the 4-hydroxythiophenol (MW 126, 1.6 g, 1.3 equivalents) followed by potassium carbonate (MW 138, 5 g, 2.0 equivalents). The reaction was heated at 65 degrees Celsius for 3 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the N,N-dimethylacetamide was removed *in vacuo*. The residue was dissolved in water (100mL) and extracted with ethyl acetate (2x). The ethyl acetate was dried over sodium sulfate and removed under reduced pressure to give the p-OH thiophenoxy compound as a crude oil. The ^1H NMR, MS, and HPLC were consistent with the desired compound.

Part B: The crude p-OH thiophenoxy compound from Part A was stirred in HCl/dioxane (50 mL) for 2 hours. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.1

g of the title compound as a yellow solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{19}NO_5S_3$: 425, found 425.

Example 115: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-aminophenyl)thiophenoxy]phenyl] sulfonyl 2H-thiopyran-4-carboxamide

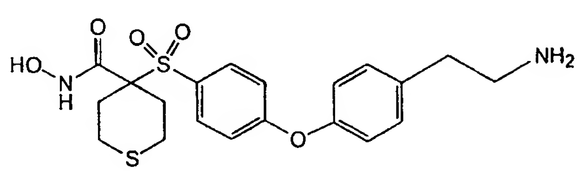


Part A: To a solution of the title compound of Example 50 (MW 402, 5 g, 1.0 equivalents) in N,N-dimethylacetamide (70 mL) was added the 4-aminothiophenol (MW 126, 1.6 g, 1.3 equivalents) followed by potassium carbonate (MW 138, 5 g, 2.0 equivalents). The reaction was heated at 65 °C for 3 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, and the N,N-dimethylacetamide was removed *in vacuo*. The residue was dissolved in water (100mL) and extracted with ethyl acetate (2x). The ethyl acetate was dried over sodium sulfate and removed under reduced pressure to give the p-NH_2 thiophenoxy compound as a crude oil. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Part B: The crude p-NH_2 thiophenoxy compound of Part A was stirred in HCl/dioxane (50 mL)

for 2 hours. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.1 g of the title compound as a yellow solid. The ^1H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{20}N_2O_4S_3$ $C_2HF_3O_2$: 538, found 538.

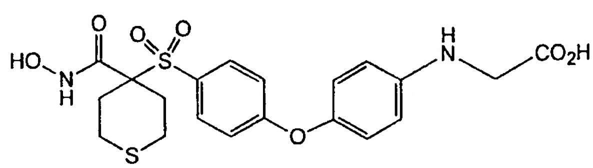
Example 116: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-tyramine)phenoxy]phenyl] sulfonyl 2H-thiopyran-4-carboxamide



Step A: To a solution of title compound of Example 50 (MW 402, 5 g, 1.0 equivalents) in N,N-dimethylacetamide (50mL) was added the trypamine (3 g, 2 equivalents), followed by cesium carbonate (10 g, 2.0 equivalents). The reaction was heated at 95 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the N,N-dimethylacetamide was removed *in vacuo*. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (TFA; pH=2), then purified on prep RPHPLC to give 2.5 g of the crude methyl ester as a yellow solid. The ^1H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The crude methyl ester from reaction Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 2.2 g of yellow foam solid as the trifluoroacetic acid salt of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{20}H_{24}N_2O_5S_2$ C2HF3O2: 550, found 550.

Example 117: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-hydroxyphenyl glycine)]phenyl] sulfonyl 2H-thiopyran-4-carboxamide

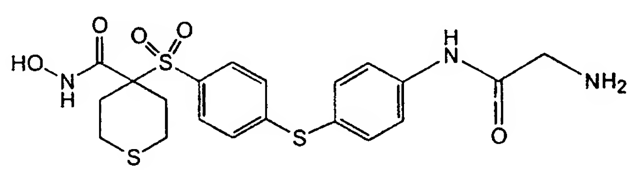


Step A: To a solution of the title compound of Example 50 (MW 402, 5 g, 1.0 equivalents) in N,N-dimethylacetamide (50 mL) was added hydroxyphenylglycine (3 g, 2 equivalents), followed by cesium carbonate (10g, 2.0 equivalents). The reaction was heated at 95 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the N,N-dimethylacetamide was removed *in vacuo*. The solvent was removed, the residue was dried and dissolved in water/acetonitrile, made acidic with

trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.0 g of the crude methyl ester as a tan solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The crude methyl ester from reaction Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.2 g of tan foam/solid as the trifluoroacetic acid salt of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{20}H_{22}N_2O_7S_2$ $C_2HF_3O_2$: 580, found 580.

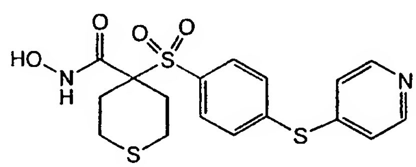
Example 118: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-hydroxyphenyl glycine)]phenyl] sulfonyl 2H-thiopyran-4-carboxamide



Step A: A solution of the title compound of Example 115 (MW 518, 2.5 g, 1.0 equivalents) in THF (25 mL)and N-Boc N-hydroxysuccinyl glycine (2.1 g, 2 equivalents) containing N-methylmorpholine (2 mL) and 4-dimethylaminopyridine (250 mg) was stirred for 12 hours. After RPHPLC indicated complete reaction at this time, the solvent was removed under

reduced pressure to give an oil. Hydrochloric acid 10% aqueous solution was added with stirring for an additional 1-2 hours. The solution was then purified on prep RPHPLC to give 1.2 g of white foam/solid as the trifluoroacetic acid salt. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. The solid was dried under reduced pressure, then suspended in ethyl ether followed by addition of 4N HCl/dioxane (20 mL). The HCl salt was filtered and washed with ethyl ether to give the title compound as a tan solid (1.1 g). The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{20}H_{23}N_3O_5S_3$ $C_2HF_3O_2$: 595, found 595.

Example 119: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)-phenyl]sulfonyl]-2H-thiopyran-4-carboxamide, monohydrochloride

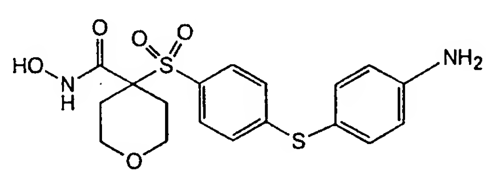


Step A: To a solution of the title compound of Example 50 (MW 402, 5 g, 1.0 equivalents) in N,N-dimethylacetamide (50 mL) were added 4-thiopyridine (3 g, 2 equivalents), followed by cesium carbonate (10g, 2.0 equivalents). The reaction mixture was heated at 75 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The

reaction mixture was filtered, and the N,N-dimethylacetamide was removed *in vacuo*. The residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.0 g of the crude -S-pyridyl THP-protected thiopyran compound as a brown solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The -S-pyridyl THP-protected thiopyran compound from Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 1.8 g of tan foam/glass as the trifluoroacetic acid salt of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{17}H_{18}N_2O_4S_3$ HCl: 447, found 447.

Example 120: Preparation of 4-[[4-[(4-aminophenyl)thio]phenyl]-sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

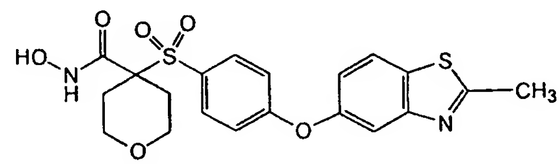


Step A: To a solution of the title compound of Example 55 (MW 387, 5 g, 1.0 equivalents)

in N,N-dimethylacetamide (50 mL) were added the 4-aminothiophenol (3 g, 2 equivalents) followed by potassium carbonate (10g, 2.0 equivalents). The reaction was heated at 60 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA was removed *in vacuo*. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 2.0 g of the crude 4-amino-S-Ph THP-protected thiopyran as a brown solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The 4-amino-S-Ph THP-protected thiopyran compound of Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give 1.4 g of tan foam/glass as the trifluoroacetic acid salt of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{20}N_2O_5S_2$: 408, found 408.

Example 121: Preparation of tetrahydro-N-hydroxy-4-[[4-[(2-methyl-5-benzothiazolyl)-oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide

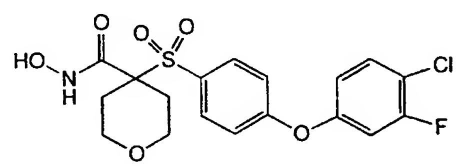


Step A: To a solution of the title compound of Example 55 (MW 387, 10g, 1.0 equivalents) in DMA (50mL) were added hydroxymethyl benzothiazole (8 g, 1.5 equivalents) followed by cesium carbonate (20 g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was cooled then filtered, the N,N-dimethylacetamide was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The desired solid separated out of solution as a gum. This gum was dissolved in ethyl aceatate (100 mL) and was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* to give an oil that was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give the 2-methyl-5-benzothiazolyloxy compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The 2-methyl-5-benzothiazolyloxy compound of Step A was stirred in aqueous HCl (20mL)/acetonitrile(20mL) for 1 hour. The solvent was concentrated and the solid that separated was filtered to give 6.5 g of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired

compound. MS (CI) M+H calculated for $C_{20}H_{20}N_2O_6S_2$: 448, found 448.

Example 122: Preparation of 4-[[4-(4-chloro-3-fluorophenoxy)phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

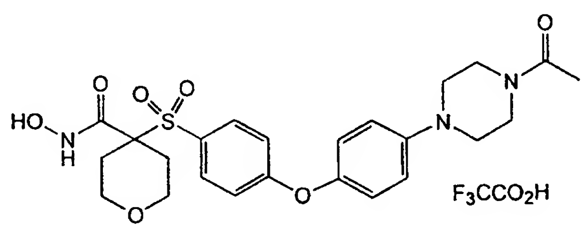


Step A: To a solution of the title compound of Example 55 (MW 387, 10 g, 1.0 equivalents) in N,N-dimethylacetamide (50 mL) were added 4-chloro-3-flourophenol (7 g, 1.4 equivalents) followed by cesium carbonate (20g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was cooled then filtered, the DMA was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The desired 4-chloro-3-fluorophenoxy compound (11 g) separated out of solution and was filtered. The ^1H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The 4-chloro-3-fluorophenoxy compound (3.4 g) of Step A was stirred in aqueous HCl (20 mL)/ acetonitrile(20 mL) for 1 hour. The solvent

was concentrated and the solid that separated was filtered to give 2.0 g of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{18}H_{17}ClFNO_6S$: 429, found 429.

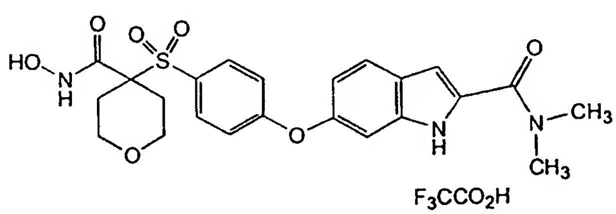
Example 123: Preparation of 4-[[4-[4-(4-acetyl-1-piperazinyl)phenoxy]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, trifluoroacetic acid salt



Step A: To a solution of the title compound of Example 55 (MW 387, 5 g, 1.0 equivalents) in DMA (50 mL) were added 1-acetyl-4-(4-hydroxy-phenyl)piperazine (3 g, 2 equivalents) followed by cesium carbonate (10g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA was removed *in vacuo*. The residue was dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 3.1 g of the crude 4-acetyl-1-piperazinylphenoxy compound as a brown solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The 4-acetyl-1-piperazinylphenoxy compound from reaction Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 2.0 g of tan foam as the trifluoroacetic acid salt of the title compound. The ^1H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{24}H_{29}N_3O_7S$ $C_2HF_3O_2$: 617, found 617.

Example 124: Preparation of N,N-dimethyl-5-[4-[[tetrahydro-4-[(hydroxyamino)-carbonyl]-2H-pyran-4-yl]sulfonyl]-phenoxy]-1H-indole-2-carboxamide, trifluoroacetic acid salt

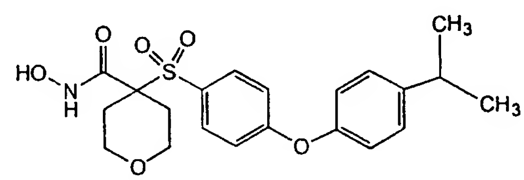


Step A: To a solution of the title compound of Example 55 (MW 387, 5g, 1.0 equivalents) in DMA (50 mL) were added the 5-hydroxy-2-indole dimethylcarboxylate (3 g, 2 equivalents) followed by Cs_2CO_3 (10 g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA was removed *in vacuo*.

The residue was dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 2.1 g of the crude THP-protected pyran hydroxamate compound as a brown solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The THP-protected pyran hydroxamate compound from Step A was stirred in aqueous HCl (50 mL) for 1hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 1.5 g of tan solid as the trifluoroacetic acid salt of the title compound. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{23}H_{25}N_3O_7S$: 487, found 487.

Example 125: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Step A: To a solution of the title compound of Example 55 (MW 387, 5 g, 1.0 equivalents) in DMA (50 mL) was added the 4-isopropylphenol (3 g, 2 equivalents), followed by cesium carbonate (10 g, 2.0 equivalents). The reaction mixture was heated at

90 degrees Celsius for 8 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA portion was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The solid (3.5 g) isopropylphenoxyphenyl THP-protected hydroxamate separated and was filtered. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound.

Step B: Into a stirred solution of aqueous HCl (20 mL) and acetonitrile (20 mL) was added the crude isopropyl-phenoxyphenyl THP-protected hydroxamate from Step A and the resulting mixture was stirred for 1-2 hours. The solvent was concentrated via a stream of nitrogen over the surface of the solution. The solid was filtered and dried to give 2.2 g of the title compound as a tan solid. The ^{1}H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $C_{21}H_{25}NO_6S$: 419, found 419.

Example 126: Preparation of Resin II:
Step 1: Attachment of Compound
<u>of Example 55, Part D, to Resin I</u>

A 500 mL round-bottomed flask was charged with of resin I [Floyd et al., *Tetrahedron Lett.* 1996, 37, 8045-8048] (8.08 g, 9.7 mmol) and 1-methyl-2-pyrrolidinone (50 mL). A magnetic stirring bar was added, and the resin slurry slowly stirred. A separate solution of the compound of Part D, Example 55 (5.58 g,19.4 mmol) in 1-methyl-2-pyrrolidinone (35

mL) was added to the slurry followed by addition of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (10.1 g, 19.4 mmol) in one portion. Once the hexafluorophosphate salt had dissolved, 4-methylmorpholine (4.26 mL, 39 mmol) was added dropwise. The reaction slurry was stirred at room temperature for 24 hours, then the resin was collected in a sintered-disc funnel and washed with N,N-dimethylformamide, methanol, methylene chloride and diethyl ether (3x30 mL each solvent). The resin was dried *in vacuo* to yield 10.99 g polymer-bound hydroxymate as a tan polymeric solid. Theoretical loading on polymer was 0.91 mmol/g. FTIR microscopy showed bands at 1693 and 3326 cm^{-1} indicative of the hydroxamate carbonyl and nitrogen-hydrogen stretches, respectively.

Step 2: Preparation of Resin III: Reaction of Resin II With Nucleophiles

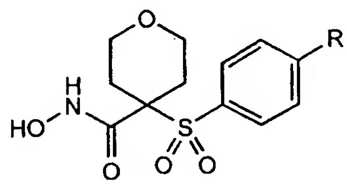
Resin II (50 mg, 0.046 mmol) was weighed into an 8 mL glass vial, and a 0.5 M solution of a nucleophile in 1-methyl-2-pyrrolidinone (1 mL) was added to the vessel. In the case of phenol and thiophenol nucleophiles, cesium carbonate (148 mg, 0.46 mmol) was added, and in the case of substituted piperazine nucleophiles, potassium carbonate (64 mg, 0.46 mmol) was added. The vial was capped and heated to 70 to 155 degrees Celsius for 24-48 hours, then cooled to room temperature. The resin was drained and washed with 1-methyl-2-pyrrolidinone, 1-methyl-2-

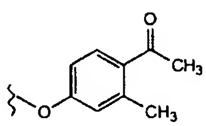
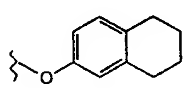
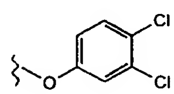
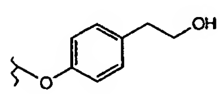
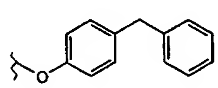
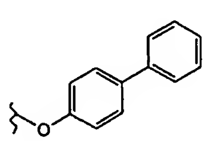
pyrrolidinone/water (1:1), water, 10% acetic acid/water, methanol, and methylene chloride (3x3 mL each solvent).

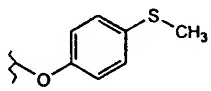
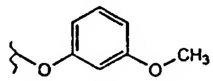
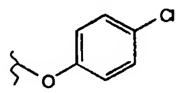
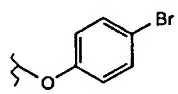
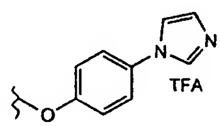
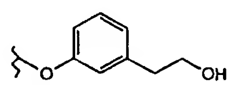
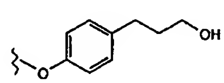
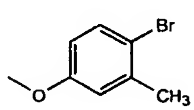
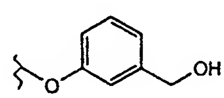
Step 3: Cleavage of Hydroxamic Acids From The Polymer-Support

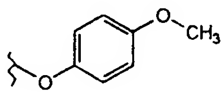
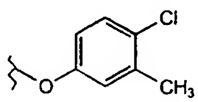
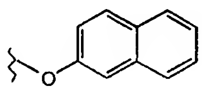
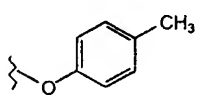
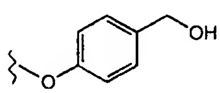
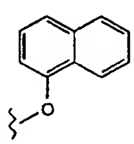
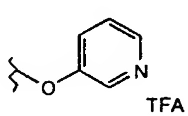
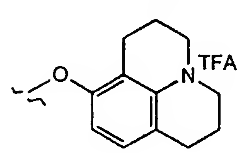
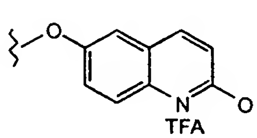
Resin III was treated with a trifluoroacetic acid/ water mixture (19:1, 1 mL) for 1 hour at room temperature. During that time, the resin became a deep red color. The resin was then drained and washed with trifluoroacetic acid/water (19:1) and methylene chloride (2x1 mL each solvent), collecting the combined filtrates in a tared vial. The volatiles were removed *in vacuo*, then a toluene/methylene chloride mixture (2 mL each) was added to the residue. The mixture was again concentrated *in vacuo*. The product was characterized by electrospray mass spectroscopy.

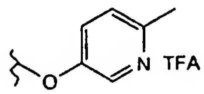
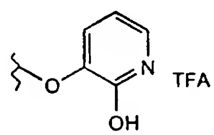
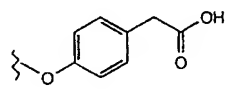
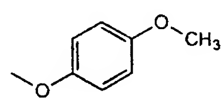
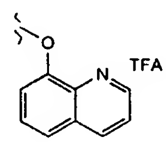
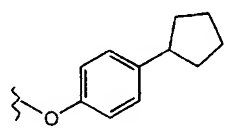
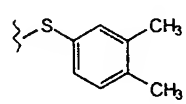
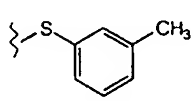
The following hydroxamic acids were synthesized from resin II using the conditions of Step 2 with the indicated nucleophile, followed by release from the polymer using Step 3 reaction conditions.

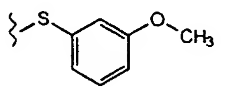
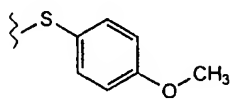
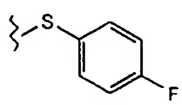
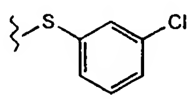
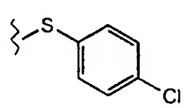
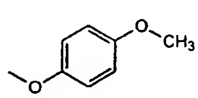
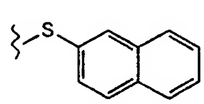
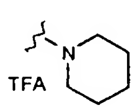


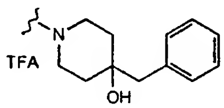
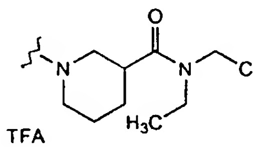
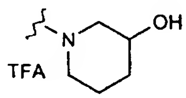
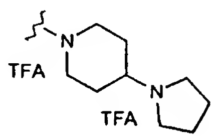
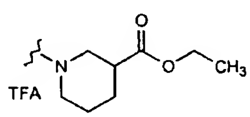
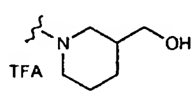
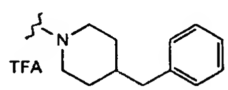
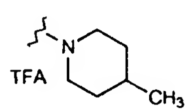
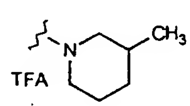
Example Number	R	Nucleophile	MS (ES) m/z
126-1		4'-hydroxy-2'-methylacetophenone	451 $(M+NH_4)$
126-2		5,6,7,8-tetrahydro-2-naphthol	455 $(M+NH_4)$
126-3		3,4-dichlorophenol	462 $(M+NH_4)$
126-4		4-hydroxyphenethyl alcohol	439 $(M+NH_4)$
126-5		4-hydroxy diphenylmethane	485 $(M+NH_4)$
126-6		4-phenylphenol	471 $(M+NH_4)$

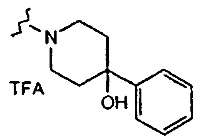
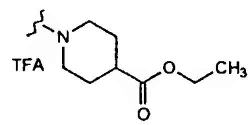
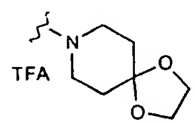
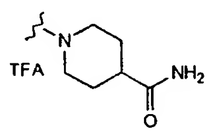
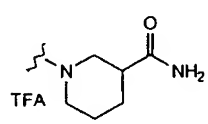
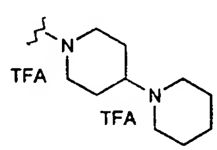
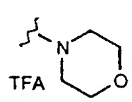
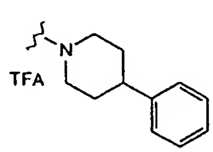
126-7		4-(methylthio)phenol	441 (M+NH_4)
126-8		3-methoxyphenol	425 (M+NH_4)
126-9		4-chlorophenol	429 (M+NH_4)
126-10		4-bromophenol	590 (M+Cs)
126-11		4-(imidazol-1-yl)-phenol	444 (M+H)
126-12		3-hydroxyphenethyl alcohol	439 (M+NH_4)
126-13		3-(4-hydroxy-phenyl)-1-phenol	453 (M+NH_4)
126-14		4-bromo-3-methylphenol	487 (M+NH_4)
126-15		3-hydroxybenzyl alcohol	425 (M+NH_4)

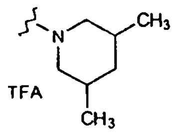
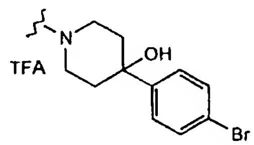
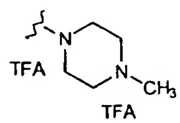
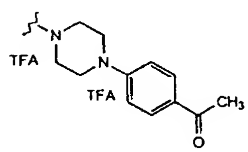
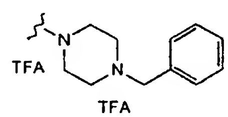
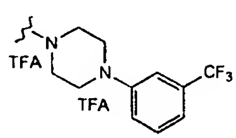
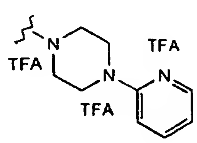
126-16		4-methoxyphenol	425 $(M+NH_4)$
126-17		4-chloro-3-methylphenol	558 (M+Cs)
126-18		2-naphthol	560 (M+Cs)
126-19		p-cresol	409 $(M+NH_4)$
126-20		4-hydroxybenzyl alcohol	408 (M+H)
126-21		1-naphthol	445 $(M+NH_4)$
126-22		3-hydroxypyridine	379 (M+H)
126-23		8-hydroxyjulolidine	473 (M+H)
126-24		2,6-quinolinediol	445 (M+H)

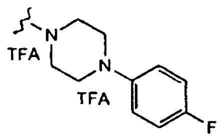
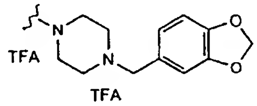
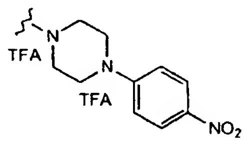
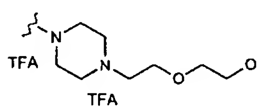
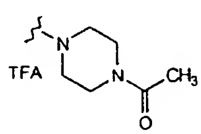
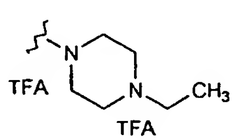
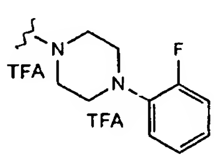
126-25		5-hydroxy-2-methylpyridine	393 (M+H)
126-26		2,3-dihydroxy-pyridine	412 (M+H)
126-27		4-hydroxyphenyl acetic acid	453 ($M+NH_4$)
126-28		4-amino-m-cresol	407 (M+H)
126-29		8-quinolinol	429 (M+H)
126-30		4-cyclopentylphenol	463 ($M+NH_4$)
126-31		3,4-dimethyl-thiophenol	439 ($M+NH_4$)
126-32		m-thiocresol	425 ($M+NH_4$)

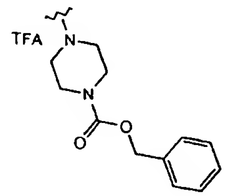
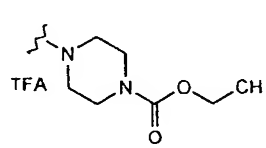
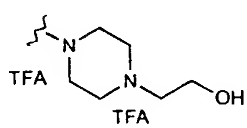
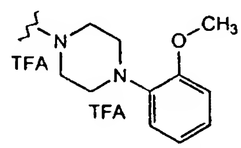
126-33		3-methoxythiophenol	441 ($M+NH_4$)
126-34		4-methoxythiophenol	441 ($M+NH_4$)
126-35		4-fluorothiophenol	429 ($M+NH_4$)
126-36		3-chlorothiophenol	445 ($M+NH_4$)
126-37		4-chlorothiophenol	445 ($M+NH_4$)
126-38		4-aminothiophenol	426 ($M+NH_4$)
126-39		2-naphthalenethiol	461 ($M+NH_4$)
126-40		piperidine	

126-41		4-benzyl-4-hydroxypiperidine	475 (M+H)
126-42		nipecotamide	468 (M+H)
126-43		3-hydroxypiperidine	385 (M+H)
126-44		4-(1-pyrrolidinyl)-piperidine	438 (M+H)
126-45		ethyl nipecotate	441 (M+H)
126-46		3-piperidinyl-methanol	512 (M+TFA)
126-47		4-benzylpiperidine	459 (M+H)
126-48		4-methylpiperidine	383 (M+H)
126-49		3-methylpiperidine	383 (M+H)

126-50		4-hydroxy-4-phenylpiperidine	461 (M+H)
126-51		ethyl isonipecotate	441 (M+H)
126-52		1,4-dioxa-8-azaspiro(4,5)decane	427 (M+H)
126-53		isonipecotamide	412 (M+H)
126-54		nipecotamide	412 (M+H)
126-55		4-piperidino-piperidine	452 (M+H)
126-56		morpholine	388 ($M+NH_4$)
126-57		4-phenylpiperidine	445 (M+H)

126-58		3,5-dimethyl-piperidine	414 (M+NH_4)
126-59		4-(4-bromophenyl)-4-piperidinol	539 (M+H)
126-60		1-methylpiperazine	384 (M+H)
126-61		4-piperazino-acetophenone	488 (M+H)
126-62		1-benzylpiperazine	460 (M+H)
126-63		N-(α,α,α-trifluoro-*m*-tolyl)piperazine	514 (M+H)
126-64		1-(2-pyridyl)-piperazine	447 (M+H)

126-65		1-(4-fluorophenyl)-piperazine	464 (M+H)
126-66		1-piperonyl-piperazine	504 (M+H)
126-67		1-(4-nitrophenyl)-piperazine	491 (M+H)
126-68		1-hydroxyethyl-ethoxypiperazine	458 (M+H)
126-69		1-acetylpiperazine	412 (M+H)
126-70		1-ethylpiperazine	398 (M+H)
126-71		1-(2-fluorophenyl)-piperazine	464 (M+H)

126-72		benzyl-1-piperazine carboxylate	504 (M+H)
126		ethyl-N-piperazine carboxylate	442 (M+H)
127		N-(2-hydroxyethyl)-piperazine	414 (M+H)
128		1-(2-methoxy-phenyl)piperazine	476 (M+H)

Example XX: Large Scale Preparation of Resin IIIa

Resin II (5 g, 0.91 mmol) was weighed into an oven-dried three-necked round bottom flask fitted with a temperature probe, an overhead stirring paddle, and a nitrogen inlet. Anhydrous 1-methyl-2-pyrrolidinone (35 mL) was added to the flask followed by ethyl isonipecotate (7.0 mL, 45.5 mmol). The resin slurry was stirred slowly with the overhead stirrer, and the mixture was heated to 80 degrees Celsius with a heating mantle for 65 hours. The flask was thereafter cooled to room temperature.

The resin was collected in a sintered-disk glass funnel and washed with N,N-dimethylformamide, methanol and methylene chloride (3X30 mL each solvent). The resin was dried *in vacuo* to provide 5.86 g of resin IIIa as off-white resin beads. The theoretical loading of the polymer was 0.81 mmol/g. TFA cleavage performed on 50 mg of resin IIIa as described in step 3 yielded 10.4 mg of off-white solid spectroscopically indistinguishable from the reaction product using ethyl isonipecotate of Example 211.

Example YY: Large Scale Preparation of Resin IIIb:

Preparation of resin IIIb followed the procedure described for preparation of resin IIIa, except ethyl nipecotate was substituted for ethyl isonipecotate. The yield after drying *in vacuo* was 5.77 g of resin IIIb as pale yellow resin beads. The theoretical loading of the polymer was 0.81 mmol/g. TFA cleavage performed on 50 mg of resin IIIb as described in step 3 yielded 14.7 mg of off-white solid spectroscopically indistinguishable from the reaction product using ethyl nipecotate of Example 212.

Step 4: Hydrolysis of Polymer-Bound Ester: Preparation of Resin IVa

Resin IIIa (5.8 g, 4.5 mmol) was weighed into a three-necked round bottomed flask fitted with an overhead stirring paddle. 1,4-Dioxane was added

to the flask, and the resin slurry was stirred for 15 minutes. Then, a 4 M solution of KOH (5 mL, 20 mmol) was added, and the mixture was stirred for 44 hours. The resin was thereafter collected in a sintered-disk glass funnel and washed with dioxane/water (9:1), water, 10% acetic acid/water, methanol and methylene chloride (3X30 mL each solvent). The resin was dried *in vacuo* to yield 5.64 g of resin IVa as off-white polymer beads. FTIR microscopy showed bands at 1732 and 1704 cm^{-1} and a broad band from 2500-3500 cm^{-1}. The theoretical loading of the polymer-bound acid was 0.84 mmol/g.

Preparation of Resin Ivb:

Using the procedure described in Step 4, resin IIIb (5.71 g, 4.5 mmol) was converted into 5.61 g of resin IVb. FTIR microscopy showed bands at 1731 and 1705 cm^{-1} and a broad band from 2500-3500 cm^{-1}. The theoretical loading of the polymer-bound acid was 0.84 mmol/g.

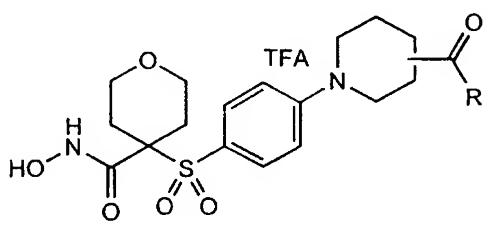
Step 5: Amide Bond Formation:

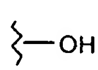
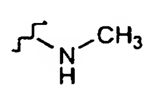
Preparation of Resin V

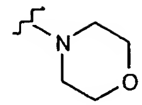
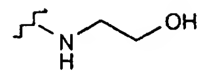
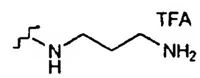
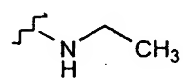
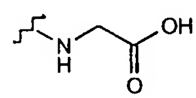
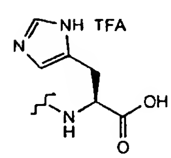
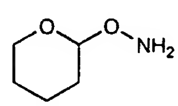
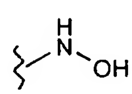
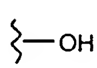
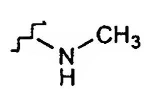
Into a fritted reaction vessel was weighed either resin IVa or resin IVb (50 mg, 0.042 mmol), and the vessel was capped under nitrogen. A 0.5 M solution of hydroxybenzotriazole in 1-methyl-2-pyrrolidinone (0.3 mL, 0.15 mmol) was added followed by a 0.5 M solution of diisopropylcarbodiimide in 1-methyl-2-pyrrolidinone (0.3 mL, 0.15 mmol). The resin was stirred using a tabletop stirring plate for

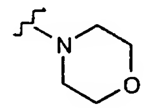
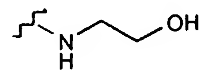
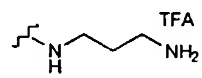
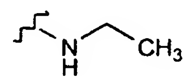
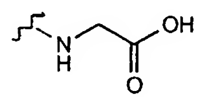
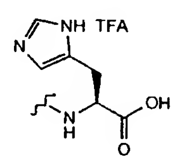
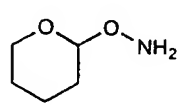
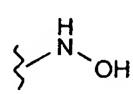
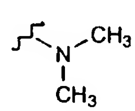
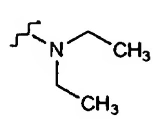
15 minutes, then a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) was added. The reaction mixture was stirred for 6 hours, then the resin was drained and washed with 1-methyl-2-pyrrolidinone (3X1mL). The reaction was repeated using the same amounts of reagents described above. The reaction mixture was stirred for 16 hours, then the resin was drained and washed with 1-methyl-2-pyrrolidinone, methanol and methylene chloride (3X1 mL each solvent).

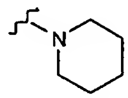
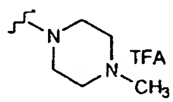
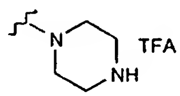
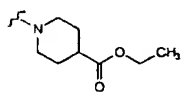
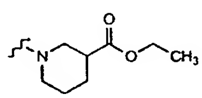
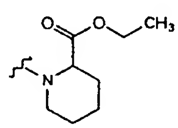
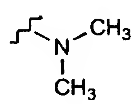
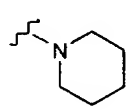
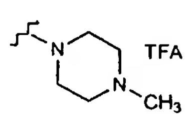
The following hydroxamic acids were synthesized using the indicated polymer-bound acid and the indicated amine in Step 5 reaction conditions followed by release from the polymer using Step 3 reaction conditions.

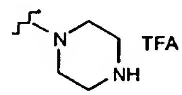
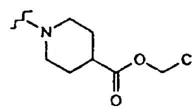
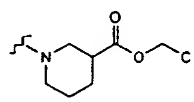
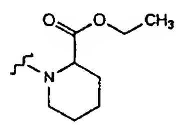
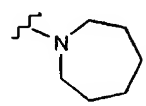
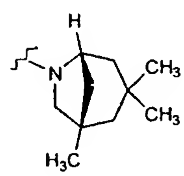
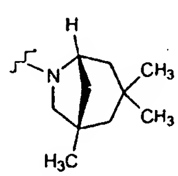


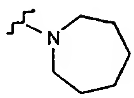
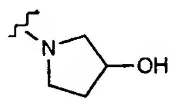
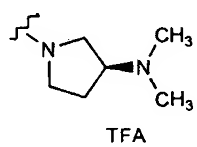
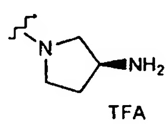
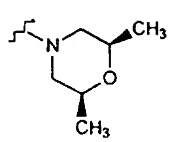
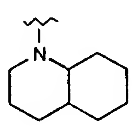
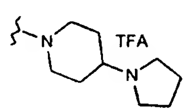
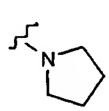
Example Number	Resin	Amine	R	Posi-tion	MS (ES) m/z
129	IVa	--------		4	
130	IVa	methylamine		4	

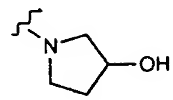
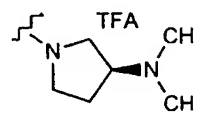
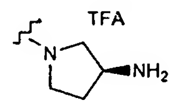
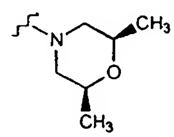
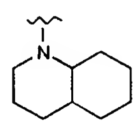
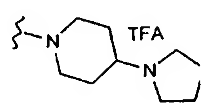
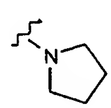
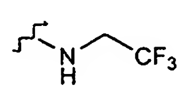
131	IVa	morpholine		4	482 (M+H)
132	IVa	ethanolamine		4	456 (M+H)
133	IVa	1,3-diamino-propane		4	469 (M+H)
134	IVa	ethylamine		4	440 (M+H)
135	IVa	glycine *t*-butyl ester HCl		4	470 (M+H)
136	IVa	L-histidine methyl ester HCl		4	564 (M+H)
137	IVa			4	428 (M+H)
138	IVb	--------		3	
139	IVb	methylamine		3	426 (M+H)
140	IVb	morpholine		3	482 (M+H)

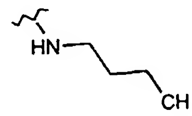
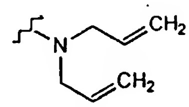
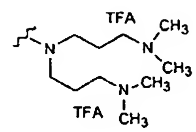
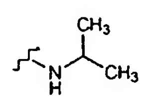
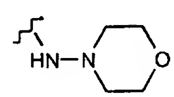
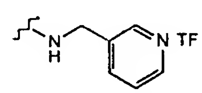
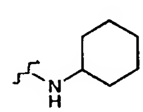
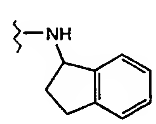
					
141	IVb	ethanolamine		3	456 M+H)
142	IVb	1,3-diamino-propane		3	469 (M+H)
143	IVb	ethylamine		3	440 (M+H)
144	IVb	glycine *t*-butyl ester HCl		3	470 (M+H)
145	IVb	L-histidine methyl ester HCl		3	564 (M+H)
146	IVb			3	428 (M+H)
147	IVa	dimethylamine		4	440 (M+H)
148	IVa	diethylamine		4	468 (M+H)

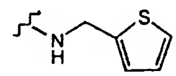
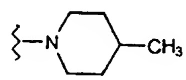
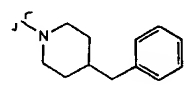
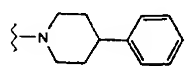
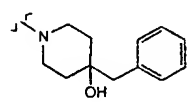
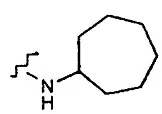
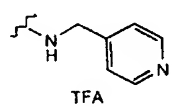
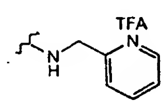
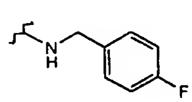
149	IVa	piperidine		4	480 (M+H)
150	IVa	1-methyl-piperazine		4	495 (M+H)
151	IVa	N-Boc-piperazine		4	481 (M+H)
152	IVa	ethyl isonipecotate		4	552 (M+H)
153	IVa	ethyl nipecotate		4	552 (M+H)
154	IVa	ethyl pipecolate		4	552 (M+H)
155	IVb	dimethylamine		3	440 (M+H)
156	IVb	piperidine		3	480 (M+H)
157	IVb	1-methyl-piperazine		3	495 (M+H)
158	IVb	N-Boc-		3	481

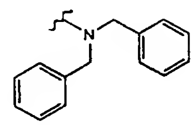
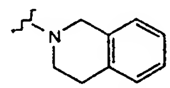
		piperazine			(M+H)
159	IVb	ethyl isonipecotate		3	552 (M+H)
160	IVb	ethyl nipecotate		3	552 (M+H)
161	IVb	ethyl pipecolate		3	552 (M+H)
162	IVb	hexamethylene-imine		3	494 (M+H)
163	IVb	1,3,3-trimethyl-6-azabicyclo [3.2.1]-octane		3	548 (M+H)
164	IVa	1,3,3-trimethyl-6-azabicyclo [3.2.1]-octane		4	548 (M+H)

165	IVa	hexamethylene-imine		4	494 (M+H)
166	IVb	3-pyrrolidinol		3	482 (M+H)
167	IVb	(3S)-(-)-3-(dimethyl amino)-pyrrolidine		3	509 (M+H)
168	IVb	(3S)-(-)-3-(t-butoxy-carbonylamino)-pyrrolidine		3	481 (M+H)
169	IVb	cis-2,6-dimethyl-morpholine		3	510 (M+H)
170	IVb	decahydro-quinoline		3	534 (M+H)
171	IVb	4-(1-pyrrolidinyl)-piperidine		3	549 (M+H)
172	IVb	pyrrolidine		3	466 (M+H)

173	IVa	3-pyrrolidinol		4	482 (M+H)
174	IVa	(3S)-(-)-3-(dimethyl amino)-pyrrolidine		4	509 (M+H)
175	IVa	(3S)-(-)-3-(*t*-butoxy-carbonylamino)-pyrrolidine		4	481 (M+H)
176	IVa	cis-2,6-dimethyl-morpholine		4	510 (M+H)
177	IVa	decahydro-quinoline		4	534 (M+H)
178	IVa	4-(1-pyrrolidinyl)-piperidine		4	549 (M+H)
179	IVa	pyrrolidine		4	466 (M+H)
180	IVa	2,2,2-tri-fluoroethyl-amine		4	494 (M+H)

181	IVa	butylamine		4	468 (M+H)
182	IVa	diallylamine		4	492 (M+H)
183	IVa	3,3'-iminobis(N,N-dimethylpropyl-amine)		4	582 (M+H)
184	IVa	iso-propylamine		4	454 (M+H)
185	IVa	4-amino-morpholine		4	497 (M+H)
186	IVa	3-(aminomethyl)-pyridine		4	503 (M+H)
187	IVa	cyclohexyl-amine		4	494 (M+H)
188	IVa	1-aminoindane		4	528 (M+H)

189	IVa	2-thiophene-methylamine		4	508 (M+H)
190	IVa	4-methyl-piperidine		4	494 (M+H)
191	IVa	4-benzyl-piperidine		4	570 (M+H)
192	IVa	4-phenyl-piperidine		4	556 (M+H)
193	IVa	4-benzyl-4-hydroxy-piperidine		4	586 (M+H)
194	IVa	cycloheptyl-amine		4	508 (M+H)
195	IVa	4-aminomethyl-pyridine		4	503 (M+H)
196	IVa	2-amino-methyl-pyridine		4	503 (M+H)
197	IVa	4-fluoro-benzylamine		4	520 (M+H)

198	IVa	dibenzylamine		4	592 (M+H)
199	IVa	1,2,3,4-tetrahydro-isoquinoline		4	528 (M+H)

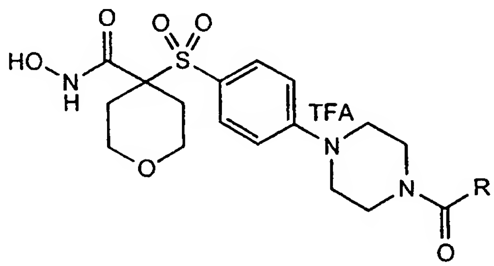
Large Scale Preparation of Resin IIIc

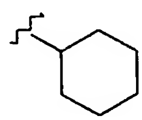
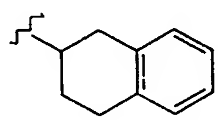
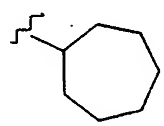
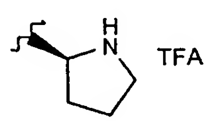
Resin II (3.01 g, 2.74 mmol) was weighed into an oven-dried three-necked round bottomed flask fitted with an overhead stirring paddle, a temperature probe and an nitrogen inlet. 1-Methyl-2-pyrrolidinone (25 mL) was added followed by piperazine (2.36 g, 27.4 mmol) and cesium carbonate (8.93 g, 27.4 mmol). Additional 1-methyl-2-pyrrolidinone (10 mL) was added, and the reaction mixture was heated to 100 degrees Celsius and stirred 18 hours. The flask was cooled to room temperature, and the resin was collected in a sintered-disc funnel and washed with N,N-diethylformamide/water (1:1), water, 10% acetic acid/water, methanol, and methylene chloride (3X30 mL each solvent). The yield after drying *in vacuo* was 3.14 g of resin IIIb as pale yellow resin beads. The theoretical loading of the polymer was 0.86 mmol/g. TFA cleavage performed on 50 mg of resin IIIb as described in Step 3 yielded 21 mg of off-white solid spectroscopically indistinguishable from the compound of Example 209.

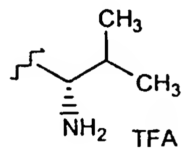
Step 6: Amide Bond Formation with resin IIIc: Preparation of Resin VI

Into a fritted reaction vessel was placed the carboxylic acid (0.215 mmol) and 1-hydroxybenzotriazole (44 mg, 0.326 mmol). The vessel was capped under nitrogen, and 1-methyl-2-pyrrolidinone was added followed by diisopropylcarbodiimide (0.034 mL, 0.215 mmol). The solution was agitated on a tabletop shaker for 15 minutes, then resin IIIc (50 mg, 0.043 mmol) was added in one portion. The reaction mixture was shaken for 16 hours, then the resin was drained and washed with 1-methyl-2-pyrrolidinone, methanol and methylene chloride (3X1 mL each solvent). In the case of N-9-fluorenyl-methoxycarbonyl-protected amino acids, the resin was further treated with a piperidine/N,N-dimethylformamide solution (1:4, 1 mL) for 30 minutes. The resin was drained and washed with N,N-dimethylformamide, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from resin IIIc using Step 6 with the indicated carboxylic acid, followed by release from the polymer using Step 3 reaction conditions.



Example Number	Carboxylic Acid	R	MS (ES) m/z
200	cyclo-hexanecarboxylic acid		502 (M+Na)
201	1,2,3,4-tetra-hydronaphthylene-2-carboxylic acid		545 ($M+NH_4$)
202	cycloheptane-carboxylic acid		511 ($M+NH_4$)
203	N-9-fluorenylmethoxy-carbonyl-L-proline		467 (M+H)

204	N-9-fluorenylmethoxy-carbonyl-L-valine		469 (M+H)

Step 7: <u>Preparation of Resin VII</u>

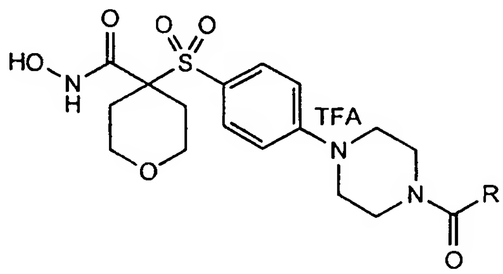
Resin IIIc (1.0g, 0.86 mmol) was weighed into an oven-dried 100 mL round-bottomed flask and a magnetic stirring bar and septum with a nitrogen needle were added. Methylene chloride (10 mL) was added, and the resin slurry was slowly stirred. *p*-Nitrophenylchloro-formate (0.867 g, 4.3 mmol) was added in one portion, followed by dropwise addition of diisopropylethylamine (0.75 mL, 4.3 mmol). A slight warming was noted with the addition. The reaction was stirred at room temperature for 18 hours, then the resin was collected in a sintered-disc glass funnel and washed with methylene chloride, methanol and methylene chloride (3X10 mL each solvent).

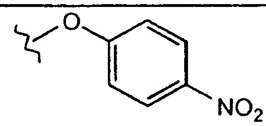
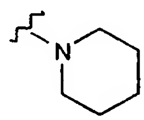
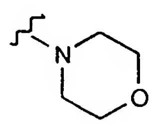
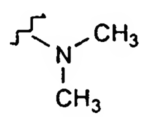
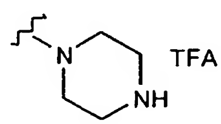
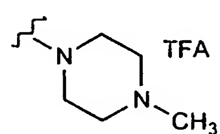
The polymer-bound product was dried *in vacuo* yielding 1.25 g of resin VII as brown resin beads. FTIR microscopy showed bands at 1798, 1733, 1696 and 1210 cm^{-1}. Theoretical loading of the polymer was 0.75 mmol/g.

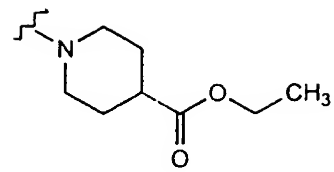
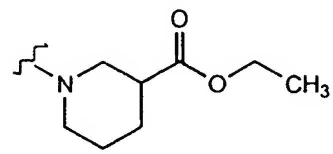
Step 8: Reaction of Resin VII with Amines Preparation of Resin VIII

An 8 mL vial was charged with resin VII (50 mg, 0.038 mmol) and a small magnetic stirring bar, and a 0.5 M solution of the amine in 1-methyl-2-pyrrolidinone (1 mL) was added. The vial was capped and heated to 50 degrees Celsius. The resin slurry was gently stirred for 15 hours, then the vial was cooled to room temperature. The resin was collected in a fritted reaction vessel and washed with 1-methyl-2-pyrrolidinone, methanol and methylene chloride (3X10 mL each solvent).

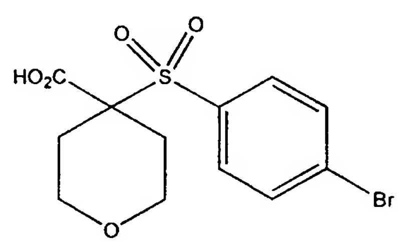
The following hydroxamic acids were synthesized from resin VII using Step 8 reaction conditions with the indicated amine, followed by release from the polymer using Step 3 reaction conditions.



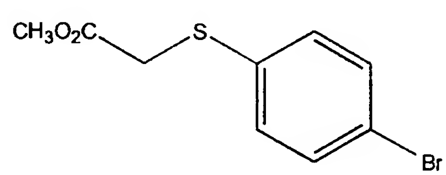
Example Number	Carboxylic Acid	R	MS (ES) m/z
205	------		535 (M+H)
206	piperidine		481 (M+H)
207	morpholine		501 (M+Na)
208	dimethylamine		441 (M+H)
209	piperazine		482 (M+H)
210	1-methyl-piperazine		496 (M+H)

211	ethyl isonipecotate		553 (M+H)
212	ethyl nipecotate		553 (M+H)

Example xxx: Preparation of 4-[(4-bromoophenyl)-sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid



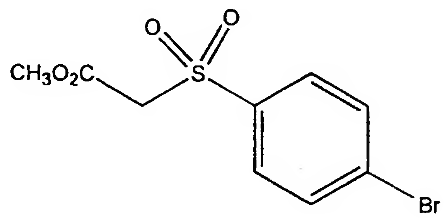
Part A: Preparatiion of



A 60% sodium hydride oil dispersion (4.0 g, 0.1 mole) was weighed into an oven-dried 3-necked 500 mL round-bottomed flask in a nitrogen glove bag, and

the flask was fitted with an nitrogen inlet, a temperature probe, an overhead stirring paddle and rubber septa. Anhydrous tetrahydrofuran (200 mL) was added to the flask, which was then cooled in an ice bath. 4-Bromothiophenol (18.91 g, 0.1 mole) was added dropwise, maintaining a temperature less than 7 degrees Celsius. Vigorous gas evolution was noted throughout addition. After complete addition, the mixture was stirred for 10 minutes with cooling. Then, methyl bromoacetate (9.5 mL, 0.1 mole) was added dropwise, maintaining a temperature less than 7 degrees Celsius. The reaction was stirred for 10 minutes with cooling, then the ice bath was removed and the mixture stirred an additional 30 minutes. The reaction was quenched by the addition of 5 mL water, then solvent was removed on rotary evaporator. The residual oil was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with 5% hydrogen choride/water (1x200 mL), saturated sodium bicarbonate (1x200 mL) and brine (1x200 mL). The organic phase was dried over magnesium sulfate and concentrated to give 24.53 g of the product as a yellow oil (94%). ^{1}H NMR was consistent with the desired structure. The mass spectrum showed an *m/z* 260 (M+H).

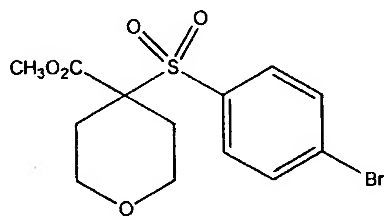
Part B: Preparation of



The compound of part A, above, (24.5 g, 0.094 mole) was weighed into a 1.0 L round-bottomed flask fitted with an overhead stirring paddle and temperature probe, then 550 mL of methanol were added, followed by 55 mL of water, causing the solution to become slightly turbid. The flask was immersed in an ice bath, and once the temperature fell below 5 degrees Celsius, Oxone®(144.5 g, 0.235 mole) was added portionwise over 5 minutes. A slight increase in temperature to 8 degrees Celsius was noted. The reaction was stirred with cooling for 10 minutes, then the ice bath was removed. After 4 hours, reversed-phase high pressure liquid chromatography showed a single component at 13.6 minutes. The reaction mixture was filtered, and the solid washed exhaustively with methanol. The combined filtrates were concentrated on a rotary evaporator, and the residual material partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (3x200 mL), saturated sodium bicarbonate (1x200 mL) and brine (1x200 mL), then the organic phase was dried over magnesium sulfate and concentrated to give 25 g of

the product as a tan solid. Trituration with hexane provided 24.3 g of pure sulfone as an off-white solid (88%). [1]H NMR was consistent with the desired structure. The mass spectrum showed an *m/z* 293 (M+H).

Part C: Preparation of



A 60% sodium hydride oil dispersion (5.76 g, 0.144 mole) was weighed into an oven-dried 3-necked 1.0 L round-bottomed flask in a nitrogen glove bag, and then the flask was fitted with an nitrogen inlet, a temperature probe, an overhead stirring paddle and rubber septa. Anhydrous N,N-dimethylformamide (250 mL) was added to the flask, mechanical stirring was initiated, and the mixture heated to 50 degrees Celsius. A solution of the compound of part B, above, (17.59 g, 0.06 mole) and dibromodiethyl ether (14.5 g, 0.06 mole) in 40 mL of N,N-dimethylformamide was added dropwise to the sodium hydride slurry, maintaining a temperature between 50-55 degrees Celsius and a steady evolution of hydrogen. After complete addition, the

temperature of the reaction mixture was increased to 65 degrees Celsius, and the mixture was stirred for 2 hours. The flask was then cooled to room temperature, and the flask was immersed in an ice bath. When the temperature fell below 20 degrees Celsius, 0.5 L ice water was added.

The mixture was transferred to a 4.0 L separatory funnel, an additional 1.0 L of water was added, and the mixture was extracted with ethyl acetate (3x200 mL). The combined organic layers were washed with 5% hydrogen chloride/water (1x200 mL), saturated sodium carbonate (1x200 mL), and brine (1x200 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 18.2 g of crude product as a yellow semi-solid. Recrystallization from ethyl acetate/hexane gave 6.53 g of pure product as tan crystals (30%). ^1H NMR was consistent with the desired structure. The mass spectrum showed an *m/z* 363 (M+H).

Part D: Preparation of the Title compound

A solution of the compound of part C, above, (4.57 g, 12.6 mmol) in 50 mL of dry tetrahydrofuran in an oven-dried 100 mL round-bottomed flask was stirred at room temperature under nitrogen, and 4.84 g of potassium trimethylsilanolate (37.7 mmol) were added in one portion. The mixture was stirred for two hours, then 10 mL of water were added dropwise. The volatiles were removed *in vacuo*, and the residue partitioned between 100 mL ethyl ether and 100 mL water. The aqueous layer was acidified to a pH value of less than 2 using

concentrated hydrogen chloride, causing a white precipitate. This mixture was extracted with ethyl acetate (3x75 mL), and the combined ethyl acetate layers were dried over magnesium sulfate and concentrated *in vacuo* to give 4.15 g of pure product as a white solid (94%). ^1H NMR ($CDCl_3/CD_3OD$) 2.10 (m, 4H), 3.28 (m, 2H), 3.90 (m, 2H), 7.60 (m, 4 H). The mass spectrum showed an *m/z* 349 (M+H).

Step 9: Attachment to Resin I: Preparation of Resin IX

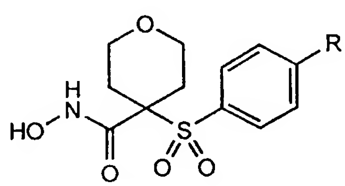
Following the procedure outlined in Step 1 before, 3.13 g of the title compound of the above preparation was reacted with 3.73 g of resin I to give 5.19 g of polymer-bound hydroxymate as a tan polymeric solid. Theoretical loading on polymer was 0.86 mmol/g. FTIR microscopy showed bands at 1693 and 3332 cm^{-1} indicative of the hydroxamate carbonyl and nitrogen-hydrogen stretches, respectively.

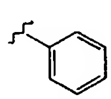
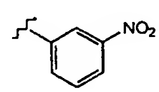
Step 10: Palladium Catalyzed Reaction of Resin IX with Boronic Acids: Preparation of Resin VII

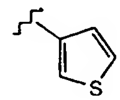
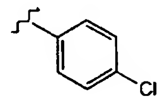
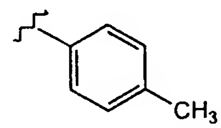
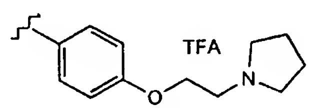
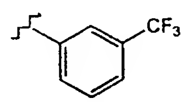
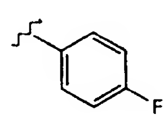
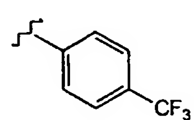
Into an 8 mL glass solid phase reaction vessel was weighed resin IX (50 mg, 0.043 mmol). The resin was washed with dry dimethoxyethane (2x3 mL). A 0.017 M solution of the palladium tetrakistriphenyl phosphine (0.6 mL, 0.01 mmol) was added to the vessel followed by a 0.6 M solution of the boronic acid in 1:1 dimethoxyethane /ethanol (0.6 mL, 0.36 mmol) and

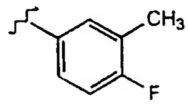
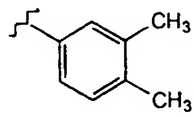
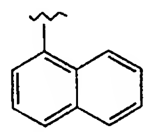
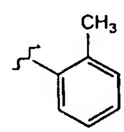
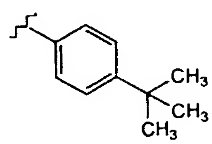
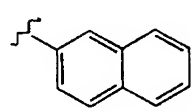
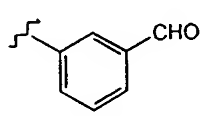
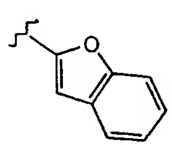
a 2M solution of potassium hydroxide in water (0.4 mL, 0.8 mmol). The vessel was maintained under a positive pressure of argon and heated at 90 degrees Celsius 16 hours. The vessel was cooled to room temperature, then the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1-methyl-2-pyrrolidinone/water (1:1), water, acetic acid/water (1:9), methanol, and methylene chloride (3x3 mL each solvent).

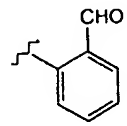
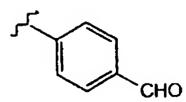
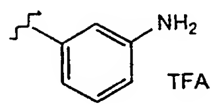
The following hydroxamic acids were synthesized from resin IX using Step 10 reaction conditions with the indicated boronic acid, followed by cleavage from the polymer using Step 3 reaction conditions.



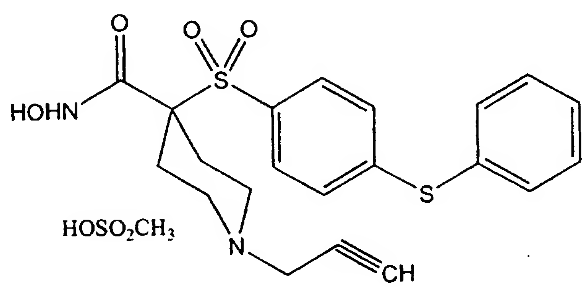
Example Number	Boronic Acid	R	MS (ES) m/z
213	phenylboronic acid		362 (M+H)
214	3-nitrophenyl-boronic acid		424 ($M+NH_4$)

215	thiophene-3-boronic acid		368 (M+H)
216	4-chlorobenzene boronic acid		413 $(M+NH_4)$
217	4-methyl-benzeneboronic acid		414 (M+K)
218	4-(2-pyrrolidinyl-ethoxy)-benzeneboronic acid		476 $(M+NH_4)$
219	3-(tri-fluoromethyl)-benzeneboronic acid		430 (M+H)
220	4-fluoro-benzeneboronic acid		418 (M+K)
221	4-(tri-fluoromethyl)-benzeneboronic acid		447 $(M+NH_4)$

222	4-fluoro-3-methylbenzene-boronic acid		411 (M+NH_4)
223	3,4-dimethyl-benzeneboronic acid		407 (M+NH_4)
224	1-naphthylene-boronic acid		412 (M+H)
225	2-methyl-benzeneboronic acid		376 (M+H)
226	4-t-butyl-benzeneboronic acid		418 (M+H)
227	2-naphthylene-boronic acid		412 (M+H)
228	3-formyl-benzeneboronic acid		390 (M+H)
229	benzofuran-2-boronic acid		419 (M+NH_4)

230	2-formyl-benzeneboronic acid		390 (M+H)
231	4-formyl-benzeneboronic acid		390 (M+H)
232	3-amino-benzeneboronic acid		377 (M+H)

Example 233: Preparation of Monomethanesulfonate salts: N-hydroxy-4-[[4-(phenylthio) phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidine-carboxamide, monomethanesulfonate



First Preparatiion

Part A: A solution of the compound of Example 9, Part J (2.1 g, 4.5 mmol) in warm H_2O (200 mL) was admixed with $NaHCO_3$ at ambient temperature. After stirring for 20 minutes, the resulting white

solid was isolated by filtration, washed with water and dried at 37 degree Celsius in a vacuum oven to afford the free base of the title compound as a white solid (1.7 g, 86%); Anal. calcd for $C_{21}H_{22}N_2O_4S_2 \cdot 0 \cdot 3\%H_2O$: C, 57.86; H, 5.23; N, 6.43; S, 14.71. Found: C,57.84; H, 4.96; N, 6.39; S, 14.89.

Part B: Methanesulfonic acid (0.28 mL, 4.1 mmol) was added to a solution of the free base of part A (1.6 g, 3.7 mmol) in methanol (10 mL) at ambient temperature. After 3 hours, the resulting solid was isolated by filtration, washed with methanol, and dried at ambient temperature in a vacuum oven to afford the monomethanesulfonate titled compound as a white solid (1.6 g, 81%): Anal. calcd for $C_{21}H_{22}N_2O_4S_2 \cdot CH_4O_3$: C,48.51; H, 5.18; N, 5.14; S, 17.66. Found: C, 48.88; H, 5.15; N, 5.23; S, 17.81.

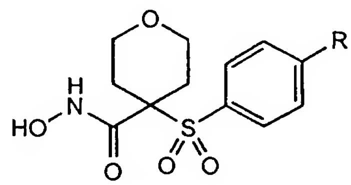
Second Preparation

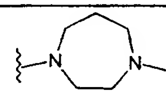
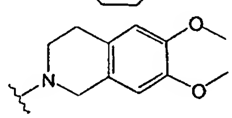
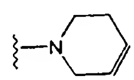
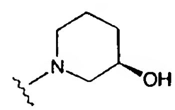
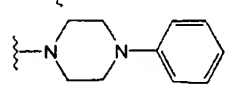
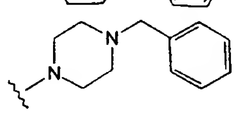
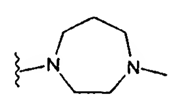
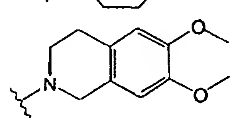
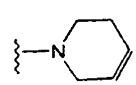
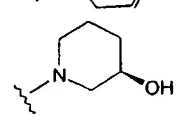
Methanesulfonic acid (0.91 mL, 14 mmol) was added to a solution of the protected hydroxamate of Example 9, Part I (6.0 g, 12 mmol) in methanol (37 mL) under a nitrogen atmosphere. After 1 hour, the precipitate was isolated by filtration, washed with methanol, and dried at 40 degrees Celsius in a vacuum oven for 1 day to afford the monomethanesulfonate title compound as a white solid (5.5 g, 89%) identical to the material from Example 233, First Preparation.

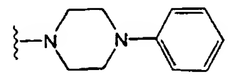
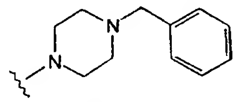
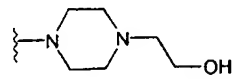
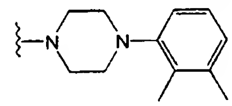
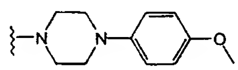
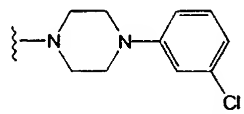
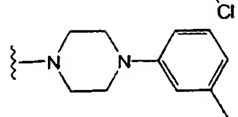
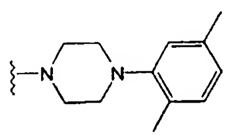
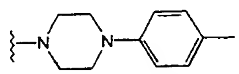
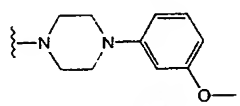
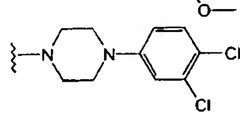
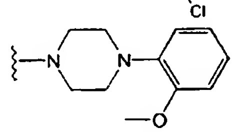
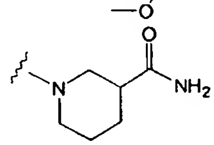
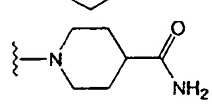
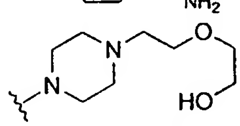
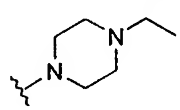
Methanesulfonate salts of the other cyclic amine compounds disclosed herein can be similarly prepared using the methods of the above two preparations.

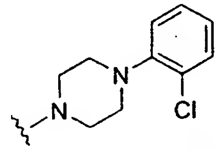
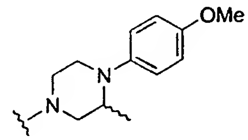
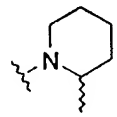
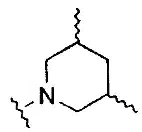
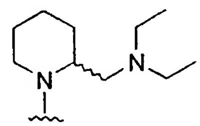
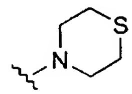
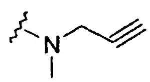
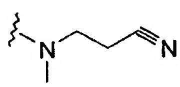
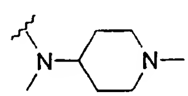
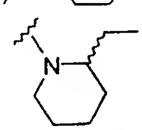
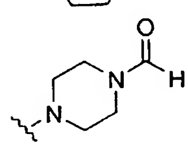
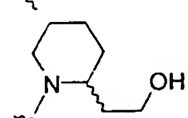
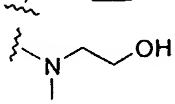
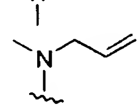
Example 234-280:

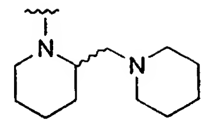
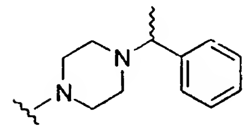
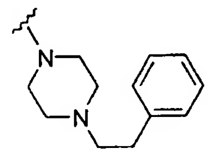
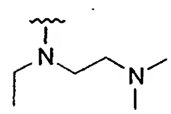
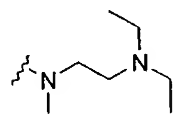
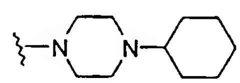
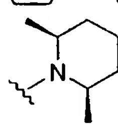
The compounds of Example 234-280 were prepared as described for the compounds of Example 129-199.



Example Number	Resin	Amine	R	Position	MS (ES) m/z
234	IVb	N-methyl homopiperazine		4	509 (M+H)
235	IVb	6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline HCl		4	588 (M+H)
236	IVb	tetrahydro-pyridine		4	478 (M+H)
237	IVb	R-3-hydroxy-piperidine HCl		4	496 (M+H)
238	IVb	phenyl-piperazine		4	557 (M+H)
239	IVb	benzyl-piperazine		4	571 (M+H)
240	IVa	methyl homopiperazine		3	509 (M+H)
241	IVa	6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline HCl		3	588 (M+H)
242	IVa	tetrahydro-pyridine		3	478 (M+H)
243	IVa	R-3-hydroxy-piperidine HCl		3	496 (M+H)

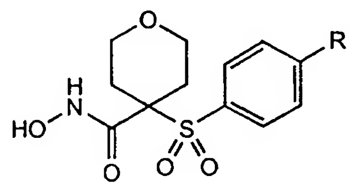
244	IVa	phenyl-piperazine		3	557 (M+H)
245	IVa	benzyl-piperazine		3	571 (M+H)
246	IVb	hydroxyethyl-piperazine		4	525 (M+H)
247	IVb	1-(2,3-xylyl)-piperazine HCl		4	585 (M+H)
247	IVb	1-(4-methoxy-phenyl)-piperazine 2HCl		4	587 (M+H)
249	IVb	1-(3-chlorophenyl)-piperazine HCl		4	591 (M+H)
250	IVb	1-(m-tolyl)-piperazine 2HCl		4	571 (M+H)
251	IVb	1-(2,5-dimethyl-phenyl)piperazine		4	585 (M+H)
252	IVb	1-(p-toyl)-piperazine 2HCl		4	571 (M+H)
253	IVb	1-(3-methoxy-phenyl)-piperazine 2HCl		4	587 (M+H)
254	IVb	1-(3,4-dichloro-phenyl)piperazine		4	625 (M+H)
255	IVb	1-(2-methoxy)-piperazine HCl		4	587 (M+H)
256	IVb	nipecotamide		4	523 (M+H)
257	IVb	isonipecotamide		4	523 (M+H)
258	IVb	1-(2-(2-hydroxy-ethoxyethyl)-piperazine		4	569 (M+H)
259	IVb	1-ethyl-piperazine		4	509 (M+H)

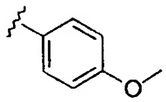
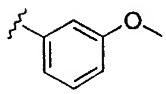
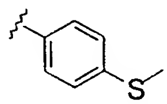
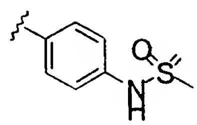
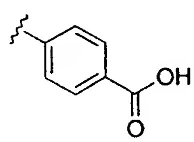
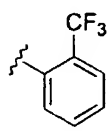
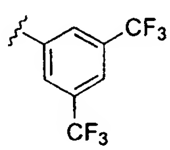
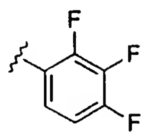
260	IVb	1-(2-chlorophenyl)-piperazine HCl		4	591 (M+H)
261	IVb	1-(4-methoxy-phenyl)-2-methyl-piperazine		4	601 (M+H)
262	IVb	2-methyl-piperidine		4	494 (M+H)
263	IVb	3,5-dimethyl-piperidine		4	508 (M+H)
264	IVb	N-(2-piperidyl-methyl)-diethylamine		4	565 (M+H)
265	IVb	thiomorpholine HCl		4	498 (M+H)
266	IVb	N-methyl-propargylamine		4	464 (M+H)
267	IVb	N-methyl-ß-alaninenitrile		4	479 (M+H)
268	IVb	1-methyl-4-(methyl-amino)piperidine		4	523 (M+H)
269	IVb	2-ethyl-piperidine		4	508 (M+H)
270	IVb	1-piperazine-carboxaldehyde		4	509 (M+H)
271	IVb	2-piperidin-ethanol		4	524 (M+H)
272	IVb	2-(methylamino)-ethanol		4	470 (M+H)
273	IVb	N-methylallyl-amine		4	466 (M+H)

274	IVb	2-(piperidino-methyl)-piperidine		4	577 (M+H)
275	IVb	1-(1-phenyl-ethyl)-piperazine		4	585 (M+H)
276	IVb	1-(2-phenyl-ethyl)-piperazine		4	585 (M+H)
277	IVb	N,N-dimethyl-N'-ethylene-diamine		4	511 (M+H)
278	IVb	N,N-diethyl-N-methylene-ethylenediamine		4	525 (M+H)
279	IVb	1-cyclohexyl-piperazine		4	563 (M+H)
280	IVb	2,6-dimethyl-piperidine		4	508 (M+H)

Example 281-288:

The following hydroxamic acids were synthesized from Resin IX using Step 10 with the indicated boronic acid, followed by cleavage from the polymer using Step 3, as discussed previously for Example 213-232:



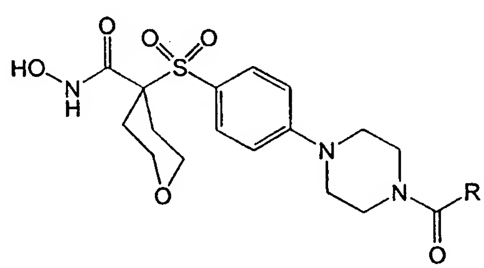
Example Number	Boronic acid	R	MS (ES) m/z
281	4-methoxy-benzeneboronic acid		392 (M+H)
282	3-methoxy-benzeneboronic acid		392 (M+H)
283	4-methylthio-benzeneboronic acid		408 (M+H)
284	4-MeNHSO$_2$-benzene boronic acid		455 (M+H)
285	4-carboxybenzene-boronic acid		406 (M+H)
286	2-trifluoromethyl-benzeneboronic acid		430 (M+H)
287	3,5-bis-(trifluoromethyl)-benzeneboronic acid		498 (M+H)
288	2,3,4-trifluoro-benzeneboronic acid		416 (M+H)

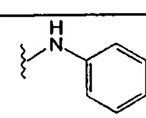
Example 289-294:

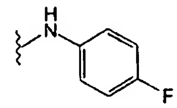
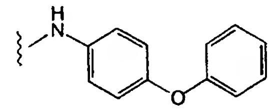
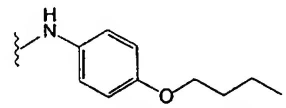
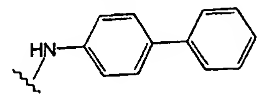
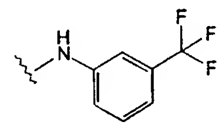
Step 11: Preparation of Resin XI.

Into a fritted reaction vessel was placed Resin IIIc (50 mg, 0.043 mmol). A 0.43 M solution of the isocyanate in 1-methyl-2-pyrrolidinone (1 mL, 0.43 mmol) was added followed by diisopropylethylamine (75 uL, 0.43 mmol). The vessel was capped under nitrogen, agitated on a tabletop shaker, and heated to 50 degrees Celsius for 48 hours. Then, the vessel was cooled to room temperature, and the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from Resin IIIc using Step 11 with the indicated isocyanate, followed by release from the polymer using the reaction conditions in Step 3.



Example Number	Isocyanate	R	MS (FAB) m/z
289	phenyl isocyanate		489.1 (M+H)

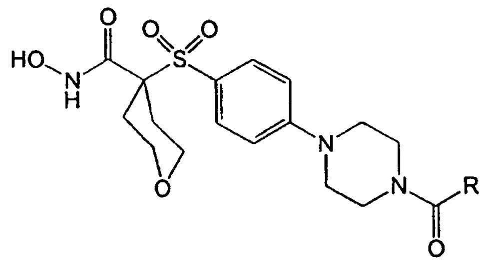
290	4-fluorophenyl isocyanate		507.2 (M+H)
291	4-phenoxyphenyl isocyanate		581.3 (M+H)
292	4-butoxyphenyl isocyanate		561.4 (M+H)
293	4-phenylphenyl-isocyanate		565.2 (M+H)
294	α,α,α-trifluoro m-tolyl ioscyanate		557.2 (M+H)

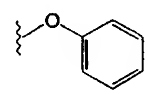
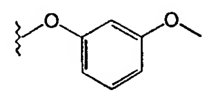
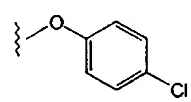
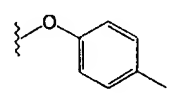
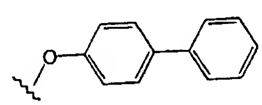
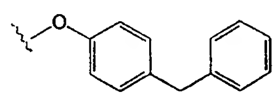
Example 295-300:

Step 12: <u>Synthesis of Resin XII.</u>

Into a fritted reaction vessel was placed resin VII (50 mg, 0.038 mmol) and cesium carbonate (122 mg, 0.38 mmol). A 0.43 M solution of the phenol in 1-methyl-2-pyrrolidinone (1 mL, 0.43 mmol) was added , then the vessel was capped under nitrogen. The reaction mixture was agitated on a tabletop shaker and heated to 50 degrees Celsius for 48 hours. Then, the vessel was cooled to room temperature, and the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from Resin IIIc using Step 11 with the indicated isocyanate, followed by release from the polymer using the reaction conditions in Step 3.



Example Number	Phenol	R	MS (FAB) m/z
295	phenol		490 (M+H)
296	3-methoxyphenol		520 (M+H)
297	4-chlorophenol		524.1 (M+H)
298	p-cresol		504.3 (M+H)
299	4-phenylphenol		566.3 (M+H)
300	4-hydroxy-diphenyl-methane		580.2 (M+H)

Example 301-323:

Large Scale Preparation of Resin Xa

A fritted reaction vessel was charged with Resin IX (1 g, 0.86 mmol) and a 0.008 M solution of tetrakis-(triphenylphosphine)palladium(0) in ethylene glycol dimethyl ether (5 mL, 0.04 mmol). A 1 M solution of 2-formylbenzeneboronic acid in a 1:1

mixture of ethanol and ethylene glycol dimethyl ether (6 mL, 6 mmol) was added followed by 1 M cesium carbonate in water (2 mL, 2 mmol). The vessel was sealed under argon and heated to 90 degrees Celsius for 16 hours. After this, the vessel was cooled to room temperature, and the resin drained and washed with the following sequence of solvents dimethylformamide, 1:1 dimethylformamide/water, dimethylformamide, water, methanol, methylene chloride (3X5 mL each solvent). The resin was dried *in vacuo* to yield 1.025 g of product as a tan polymeric solid. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 35 mg of Resin Xa as described in Step 3 yielded 11.2 mg of a tan solid

Large Scale Preparation of Resin Xb.

Preparation of Resin Xb followed the identical procedure described for preparation of resin Xa, except 3-formylbenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The yield after drying *in vacuo* was 1.052 g of Resin Xb as tan resin beads. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 20 mg of Resin Xb as described in Step 3 yielded 6.5 mg of a tan solid.

Large Scale Preparation of Resin Xc.

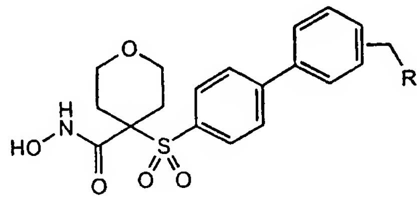
Preparation of Resin Xc followed the identical procedure described for preparation of resin Xa, except 4-formylbenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The yield after drying *in vacuo* was 1.03 g of Resin Xc as tan resin

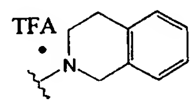
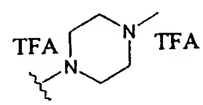
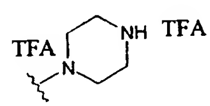
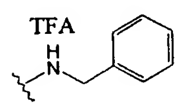
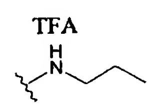
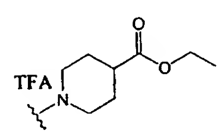
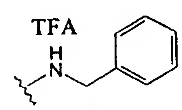
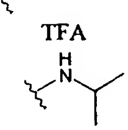
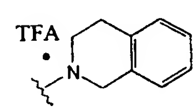
beads. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 28 mg of Resin Xb as described in Step 3 yielded 9.4 mg of a tan solid.

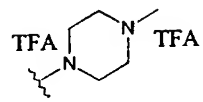
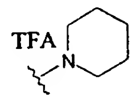
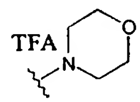
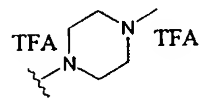
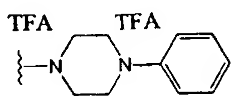
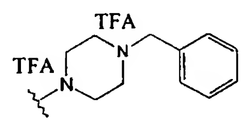
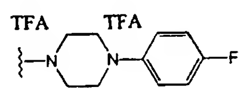
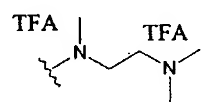
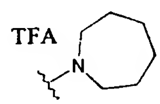
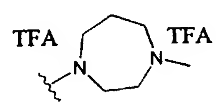
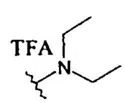
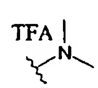
Step 13: Synthesis of Resin XIII.

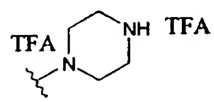
Into a fritted reaction vessel was placed resin Xa, Xb or Xc (50 mg, 0.042 mmol). A 0.2 M solution of the amine in trimethylorthoformate (1 mL, 0.2 mmol) was added, and the vessel was capped under nitrogen. The reaction mixture was agitated on a tabletop shaker for 3 hours. Then, a 0.5 M solution of sodium triacetoxyborohydride in 1-methyl-2-pyrrolidinone (0.8 mL, 0.4 mmol) was added to the vessel, and the mixture was agitated an additional 40 hours. After this, the resin was drained and washed (3X1 mL each solvent) with the following sequence of solvents: 1-methyl-2-pyrrolidinone, methanol, water, methanol and methylene chloride.

The following hydroxamic acids were synthesized using the indicated resin-bound aldehyde and the indicated amine following the procedure outlined in Step 13 followed by release from the polymer using the procedure in Step 3:



Example Number	Resin	Amine	R	posi-tion	MS (ES) m/z
301	Xb	1,2,3,4-tetrahydro-isoquinoline		3	507 (M+H)
302	Xb	1-methyl-piperazine		3	474 (M+H)
303	Xb	piperazine		3	460 (M+H)
304	Xb	benzylamine		3	481 (M+H)
305	Xb	propylamine		3	433 (M+H)
306	Xb	ethyl iso-nipecotate		3	531 (M+H)
307	Xa	benzylamine		2	481 (M+H)
308	Xa	isopropyl-amine		2	433 (M+H)
309	Xa	1,2,3,4-tetrahydro-isoquinoline		2	507 (M+H)

310	Xa	1-methyl-piperazine		2	474 (M+H)
311	Xc	piperidine		4	459 (M+H)
312	Xc	morpholine		4	461 (M+H)
313	Xc	1-methyl-piperazine		4	474 (M+H)
314	Xc	1-phenyl-piperazine		4	536 (M+H)
315	Xc	1-benzyl-piperazine		4	550 (M+H)
316	Xc	1-(4-fluoro-phenyl)-piperazine		4	554 (M+H)
317	Xc	N,N,N'-trimethyl-ethylenediamine		4	476 (M+H)
318	Xc	hexamethyl-eneimine		4	473 (M+H)
319	Xc	1-methyl-homopiperazine		4	488 (M+H)
320	Xc	diethylamine		4	447 (M+H)
321	Xc	pyrrolidine		4	445 (M+H)
322	Xb	dimethylamine		3	419 (M+H)

323	Xc	1-t-butoxy-carbonyl-piperazine		4	460 (M+H)

Large Scale Preparation of Resin Xd

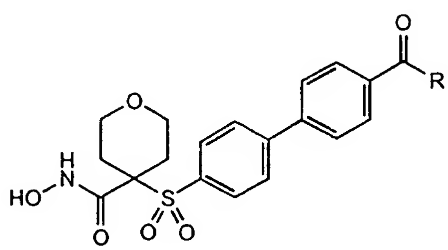
Preparation of Resin Xd followed the identical procedure described for preparation of resin Xa, except 4-carboxybenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The yield after drying *in vacuo* was 1.07 g of Resin Xd as a tan polymeric solid. The theoretical loading of the polymer was 0.83 mmol/g. TFA cleavage performed on 23.5 mg of Resin Xd as described in Step 3 yielded 4.9 mg of a tan solid.

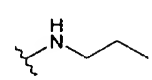
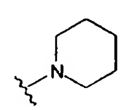
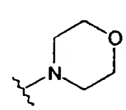
Step 14: Synthesis of Resin XIV

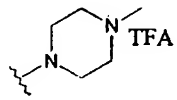
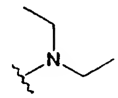
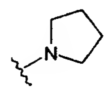
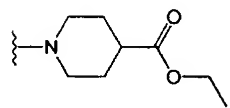
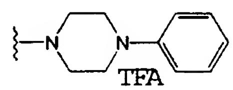
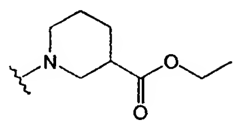
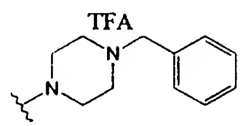
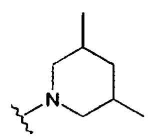
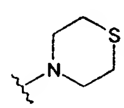
Into a fritted reaction vessel was placed resin Xd (50 mg, 0.042 mmol). The resin was washed with 1-methyl-2-pyrrolidinone (2X3 mL), then a 1.0 M solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate in 1-methyl-2-pyrrolidinone (0.2 mL, 0.2 mmol) was added, followed by a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) and a 1.0 M solution of the diisopropylethylamine in 1-methyl-2-pyrrolidinone (0.4 mL, 0.4 mmol). The vessel was capped under nitrogen, and the reaction mixture was agitated on a tabletop shaker for 24 hours. Then, the resin was drained and washed with 1-methyl-2-pyrrolidinone (3X1 mL). The reaction with the amine was repeated by addition of a 1.0 M solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium

hexafluorophosphate in 1-methyl-2-pyrrolidinone (0.2 mL, 0.2 mmol), a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) and a 1.0 M solution of the diisopropylethylamine in 1-methyl-2-pyrrolidinone (0.4 mL, 0.4 mmol). The vessel was capped under nitrogen, and the reaction mixture was agitated an additional 8 hours. Then, the resin was drained and washed with the following sequence of solvents: 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water, water, 1:9 acetic acid/water, methanol, methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized using Resin Xd and the indicated amine following the procedure outlined in Step 14 followed by release from the polymer using the procedure in Step 3:



Example	amine	R	MS (ES) m/z
324	propylamine		447 (M+H)
325	piperidine		473 (M+H)
326	morpholine		475 (M+H)

327	1-methyl-piperazine		488 (M+H)
328	diethylamine		461 (M+H)
329	pyrrolidine		459 (M+H)
330	ethyl isonipecotate		545 (M+H)
331	1-phenyl-piperazine		550 (M+H)
332	ethyl nipecotate		545 (M+H)
333	1-benzyl-piperazine		564 (M+H)
334	3,5-dimethyl-piperidine		501 (M+H)
335	thiomorpholine hydrochloride		491 (M+H)

Example 336: Preparation of 4-[[4-[4-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-1-piperidinyl]-phenyl] sulfonyl] tetrahydro-2H-pyran-4-carboxylic acid

Part A: To a solution of the product of Example 11, Part B (10.0 g, 34.7 mmol) in 1-methyl-2-pyrrolidinone (70 mL) was added 4-(N-t-

butoxycarbonylamino)piperidine (10.43 g, 52.1 mmol), followed by diisopropylethylamine (6.0 mL, 34.7 mmol). The resulting mixture was heated at 80 degrees Celsius for 24 hours and then cooled to room temperature. The crude mixture was poured into 700 mL water, and the cloudy aqueous layer was extracted with ethyl acetate (3X150 mL). The combined organic layers were washed with 5% potassium hydrogen sulfate (2X150 mL) and brine (2X150 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give the crude ester as a white foamy solid (13.04 g, 78%).

Part B: To a solution of the ester of part A (5.74 g, 11.9 mmol) in a mixture of ethanol (80 mL) and tetrahydrofuran (40 mL) was added 2 N sodium hydroxide (60 mL; 120 mmole). The resulting solution was heated to 60 degrees Celsius for 1 hour and then cooled to room temperature. The solution was concentrated *in vacuo*, and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The aqueous layer was separated and acidified with concentrated hydrogen chloride to pH 2. A white precipitate formed, which was collected by vacuum filtration and dried *in vacuo* to give the carboxylic acid as a white solid (4.88 g, 88%).

Part C: To a suspension of the carboxylic acid from part B (4.88 g, 10.4 mmol) in methylene chloride (35 mL) was added trifluoroacetic acid (35 mL), resulting in dissolution of the solid. After fifteen minutes at ambient temperature, the solution was concentrated *in vacuo*. The product was triturated with diethyl ether to give the amino acid as an off-white solid (4.92 g, 98%).

Part D: A suspension of the amino acid from part C (4.92 g, 10.21 mmol) in a mixture of 10% sodium carbonate/water (35 mL), water (100 mL) and dioxane (100 mL) was cooled in an ice bath. To the cooled suspension is added a solution of 9-fluorenylmethylsuccinimidyl carbonate (3.79 g, 11.23 mmol) in dioxane (50 mL) dropwise. After complete addition, the ice bath was removed, and the mixture warmed to room temperature. After one hour, the solution was concentrated *in vacuo*, and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The aqueous layer was separated and acidified with concentrated hydrogen chloride to pH 2. The white precipitate formed, which was collected by vacuum filtration, washed with hexanes and dried *in vacuo* to give the title compound as a white solid (5.46 g, 91%).

<u>Step 15: Preparation of Resin XVI.</u>

Part A: Following the procedure outlined in Step 1 above, the product of Example 336 (2.4 g, 4.06 mmol) was reacted with Resin I (1.7 g, 2.03 mmol) to give Resin XV as a tan polymeric solid (2.82 g). Theoretical loading on polymer was 0.71 mmol/g.

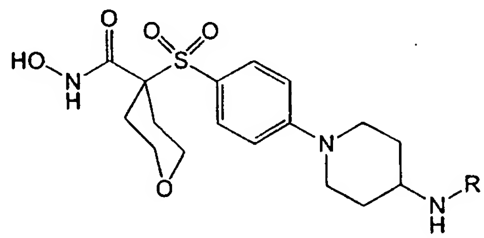
Part B: Resin XV from part A above (2.76 g, 1.96 mmol) was suspended in a 1:4 piperidine/ dimethylformamide solution (20 mL) in a fritted reaction vessel and agitated on a tabletop shaker for 5 minutes. The resin was drained, and an additional volume of a 1:4 mixture of piperidine/dimethylformamide (20 mL) was added to the vessel. The slurry was agitated at room temperature for 30 minutes. After this, the resin was drained

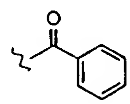
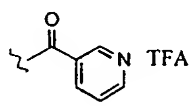
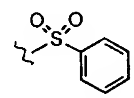
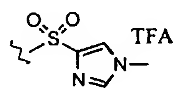
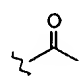
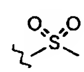
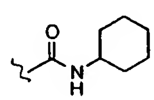
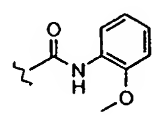
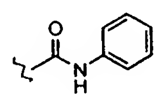
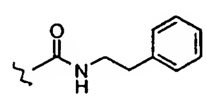
and washed with dimethylformamide, methanol, and methylene chloride (3X20 mL each solvent). After drying *in vacuo*, the title resin was obtained as a tan polymeric solid (2.30 g).

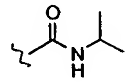
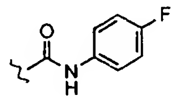
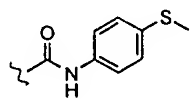
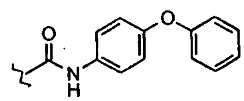
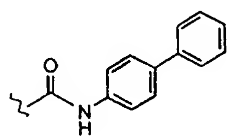
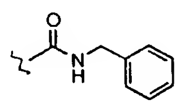
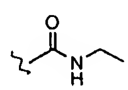
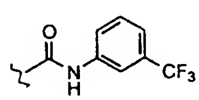
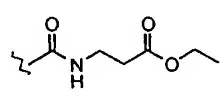
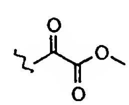
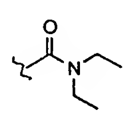
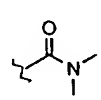
Step 16: Acylation/Sulfonylation of Resin XVI.

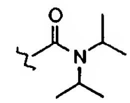
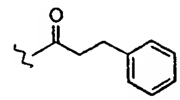
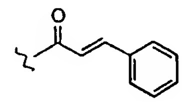
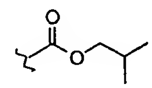
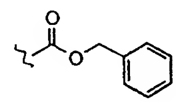
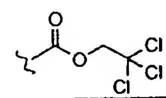
In a fritted reaction vessel, Resin XVI (50 mg, 0.043 mmol) was washed with 1-methyl-2-pyrrolidinone (2X1 mL). Then, a 0.22 M solution of the acylating or sulfonylating reagent in 1-methyl-2-pyrrolidinone (1 mL, 0.22 mmol) was added to the resin followed by diisopropylethylamine (40 uL, 0.22 mmol). The vessel was capped under nitrogen and agitated on a tabletop shaker at room temperature for 16 hours. Then, the resin was drained and washed with 1-methyl-2-pyrrolidinone, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from Resin XVI using Step 16 with the indicated acylating or sulfonylating reagent, followed by release from the polymer using the reaction conditions in Step 3.



Example	Acylating or Sulfonylating Reagent	R	MS (ES) m/z
337	benzoyl chloride		488.2(M+H)
338	nicotinyl chloride-HCl		489.2(M+H)
339	benzenesulfonyl chloride		462(M+H)
340	1-methyl-imidazole-4-sulfonyl chloride		528.2(M+H)
341	acteyl chloride		426.2(M+H)
342	methanesulfonyl chloride		462.1(M+H)
343	cyclohexyl isocyanate		509 (M+H)
344	2-methoxyphenyl isocyanate		533 (M+H)
345	phenyl isocyanate		503 (M+H)
346	beta-phenylethyl isocyanate		531 (M+H)

347	isopropyl isocyanate		469 (M+H)
348	4-fluorophenyl isocyanate		521 (M+H)
349	4-(methylthio)-phenyl isocyanate		549 (M+H)
350	4-phenoxyphenyl isocyanate		595 (M+H)
351	4-phenylphenyl isocyanate		579 (M+H)
352	benzyl isocyanate		517 (M+H)
353	ethyl isocyanate		455 (M+H)
354	alpha,alpha,alpha-trifluoro-m-tolyl isocyanate		571 (M+H)
355	ethyl 3-isocyanato-propionate		527 (M+H)
356	methyl oxalyl chloride		470 (M+H)
357	diethylcarbamyl chloride		483 (M+H)
358	dimethylcarbamyl chloride		455 (M+H)
359	diisopropyl carbamyl chloride		511 (M+H)

			
360	hydrocinnamoyl chloride		516 (M+H)
361	cinnamoyl chloride		514 (M+H)
361	isobutyl-chloroformate		484 (M+H)
363	benzylchloro-formate		518 (M+H),
364	trichloroethyl-chloroformate		558 (M+H)

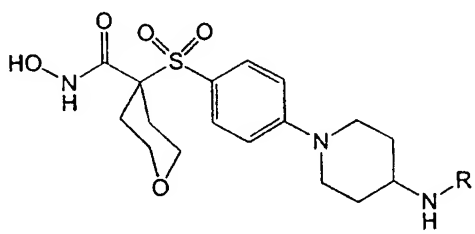
Example 365-371:

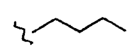
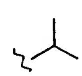
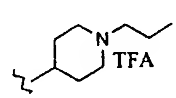
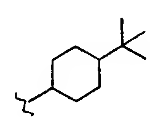
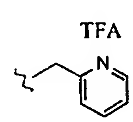
Step 17: Reductive Alkylation of Resin XVI.

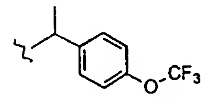
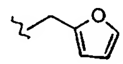
In a fritted reaction vessel, Resin XVI (50 mg, 0.043 mmol) was washed methylene chloride (2X1 mL). Then, a 1 M solution of the aldehyde or ketone in methylene chloride (1 mL, 1 mmol) was added to the resin. The vessel was capped under nitrogen and agitated on a tabletop shaker at room temperature for 3 hours. The resin was drained and washed with methylene chloride (3X1 mL). Then, the resin was retreated with the 1 M solution of the aldehyde or ketone in methylene chloride (1 mL, 1 mmol). The resin was drained and washed with methylene chloride (3X1 mL each solvent). Then, a 1 M solution of

sodium triacetoxyborohydride in 1-methyl-2-pyrrolidinone (1 mL, 1 mmol) was added to the resin, and the reaction was stirred overnight. After this, the resin was drained and washed with 1-methyl-2-pyrrolidinone, methanol, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

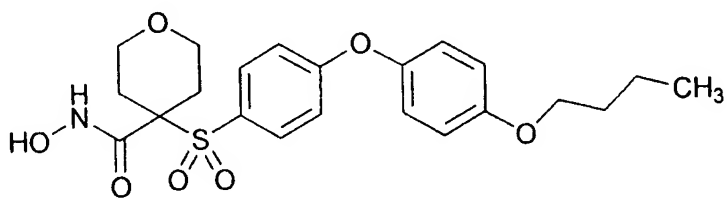
The following hydroxamic acids were synthesized from Resin XVI using Step 17 with the indicated aldehyde or ketone, followed by release from the polymer using the conditions in Step 3.



Example Number	Aldehyde or Ketone	R	MS (ES) m/z
365	butyraldehyde		440 (M+H)
366	acetone		426 (M+H)
367	N-propyl-4-pyridone		509 (M+H)
368	4-t-butylcyclo-hexanone		522 (M+H)
369	2-pyridine-carboxaldehyde		475 (M+H)

370	4'-(trifluoro-methoxy)-acetophenone		572 (M+H)
371	2-furaldehyde		464 (M+H)

Example 372: Preparation of 4-[[4-(4-butoxyphenoxy)-phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

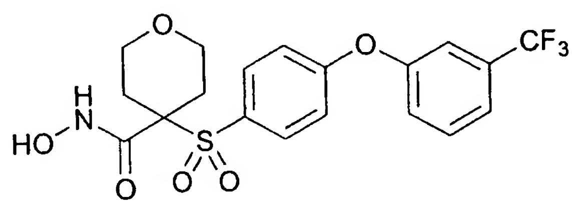


Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and 4-butoxyphenol (2.66 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for nineteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as an off-white foam (3.96 g, 93%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{27}H_{35}N_1O_8\ S_1F$: 551.24, found 551.24.

Part B: To a solution of the THP hydroxamate from part A (3.9 g, 7.3 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20

mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.75 g, 84%). HRMS (ES+) M+ H $^+$ calculated for $C_{22}H_{27}N_1O_7S_1$: 450.16, found 450.16.

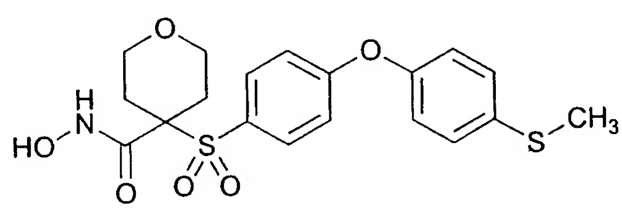
Example 373: Preparation of tetrahydro-N-hydroxy-4-[[4-[3-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and m-(trifluoromethyl)phenol (1.95 mL, 16 mmol). The slurry was stirred at ninety five degrees Celsius for nineteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.1 g, 97%). HRMS (ES+) $M+H^+$ calculated for $C_{24}H_{26}N_1O_7$ S_1F_3 : 530.15, found 530.14.

Part B: To a solution of the THP hydroxamate from part A (3.9 g, 7.4 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.9 g, 58%). HRMS (ES+) $M+H^+$ calculated for $C_{19}H_{18}N_1O_6S_1F_3$: 446.09, found 446.09.

Example 374: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(methylthio)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide

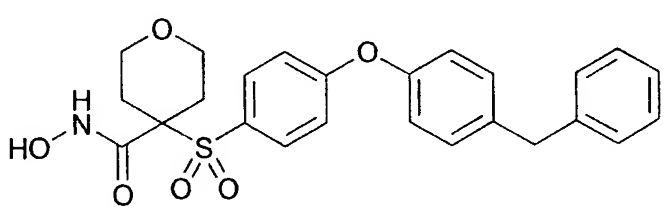


Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and 4-(methylthio)phenol (2.24 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for twenty four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.1 g, 100%). HRMS (ES+)

M+H$^+$ calculated for $C_{24}H_{29}N_1O_7S_2$: 508.15, found 508.15.

Part B: To a solution of the THP hydroxamate from part A (4.0 g, 7.9 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.9 g, 57%). HRMS (ES+) M+ H$^+$ calculated for $C_{19}H_{21}N_1O_6S_2$: 424.09, found 424.09.

Example 375: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(phenylmethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide

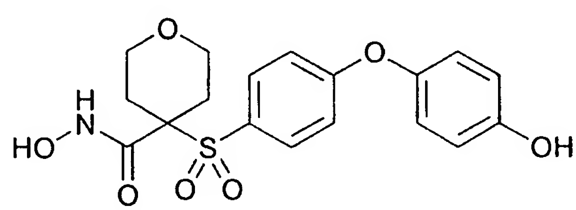


Part A: To a solution of the product of Example 55 (2.7 g, 7 mmol) in dimethylacetamide (15 mL) was added cesium carbonate (6.84 g, 21 mmol) and 4-hydroxydiphenylmethane (2.8 g, 14 mmol). The slurry was stirred at ninety degrees Celsius for nineteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica,

ethyl acetate/hexanes) provided the substituted THP hydroxamate as a light yellow foam (3.7 g, 96%). HRMS (ES+) M+H$^+$ calculated for $C_{30}H_{33}N_1O_7S_1$: 552.21, found 552.21.

Part B: To a solution of the THP hydroxamate from part A (3.5 g, 6.4 mmol) in 1,4-dioxane (16 mL) was added 4N HCl dioxane solution (16 mL) and methanol (16 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.95 g, 67%). HRMS (ES+) M+H$^+$ calculated for $C_{25}H_{25}N_1O_6S_1$: 468.15, found 468.15.

Example 376: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-hydroxyphenoxy)phenyl]sulfonyl]-2H-pyran-4-carboxamide

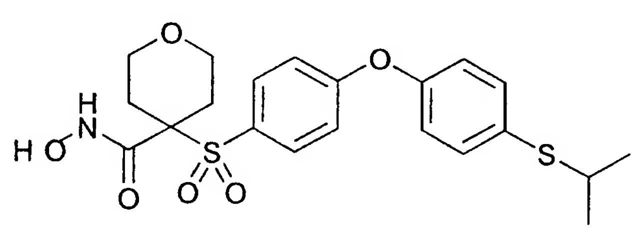


Part A:To a solution of the product of Example 55) (2.7 g, 7 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (6.84 g, 21 mmol) and 4-(benzyloxy)phenol (2.8 g, 14 mmol). The slurry was stirred at ninety five degrees Celsius for six hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine,

dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (3.94 g, 99%). HRMS (ES+) M+ NH_4^+ calculated for $C_{30}H_{33}N_1O_8$ S_1 : 585.23, found 585.23.

Part B: To a solution of the THP hydroxamate from part A (1.5 g, 2.64 mmol) in glacial acetic acid (5 mL) was added concentrated HCl (5 mL) and the reaction was heated to sixty degrees Celsius for twenty minutes. The reaction was cooled, diluted with water (100 mL) and extracted with ethyl acetate. The ethyl acetate extract was washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (810 mg, 78%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{18}H_{19}N_1O_7S_1$: 468.15, found 468.15.

Example 377: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-[(1-methylethyl)thio]phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a suspension of 4-hydroxythiophenol (5.0 g, 40 mmol) and potassium

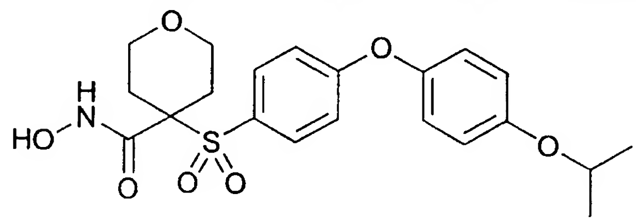
carbonate (8.0 g, 58 mmol) in dimethylformamide (70 mL) was added 2-iodopropane (7.0 g, 41 mmol). The slurry was stirred at ambient temperature for one hour. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed two times with water, 10% HCl solution, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted phenol as a clear colorless oil (5.1 g, 76%).

Part B: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and the phenol from part A (2.7 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for fifteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.15 g, 97%). HRMS (ES+) $M+H^+$ calculated for $C_{26}H_{33}N_1O_7S_2$: 536.18, found 538.17.

Part C: To a solution of the THP hydroxamate from part A (3.9 g, 7.3 mmol) in 1,4-dioxane (18 mL) was added 4N HCl dioxane solution (18 mL) and methanol (18 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as an off white solid (2.32 g,

71%). HRMS (ES+) M+ H $^+$ calculated for $C_{21}H_{25}N_1O_6S_2$: 452.12, found 452.12.

Example 378: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy)phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of benzoic acid, 4-hydroxyphenylester (8.57 g, 40 mmol) in dimethylacetamide (65 mL) was added potassium carbonate (8.3 g, 60 mmol) and 2-iodopropane (5 mL, 50 mmol). The slurry was stirred at sixty five degrees Celsius for one hour. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the isopropoxy compound as a light gray solid (9.7g, 95%).

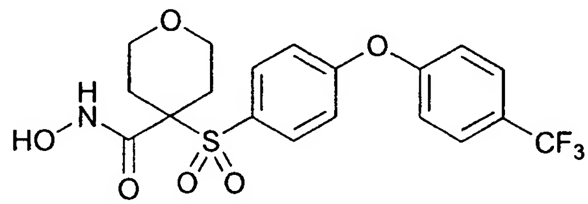
Part B: To a slurry of the isopropoxy compound from part A (9.7 g, 38 mmol) in 1,4-dioxane (20 mL) and water (20 mL) was added 2.5N sodium hydroxide solution (26 mL, 65 mmol). The slurry was stirred at sixty degrees Celsius for four hours. The reaction was cooled and 6N hydrochloric acid solution was added until the pH=5. The reaction was extracted with methylene chloride. The organic layer was washed with 5% ammonium hydroxide solution four times, water, brine, dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to yield the phenol as an amber oil (5.4 g, 94%).

Part C: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and the phenol from part B (2.4 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for twenty one hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as an off white foam (3.65 g, 88%). HRMS (ES+) M+ H^+ calculated for $C_{26}H_{33}N_1O_8S_1$: 520.20, found 520.20.

Part D: To a solution of the THP hydroxamate from part C (3.5 g, 6.7 mmol) in 1,4-dioxane (17 mL) was added 4N HCl dioxane solution (17 mL) and methanol (17 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as an off white solid (2.2 g, 80%). HRMS (ES+) M+ H^+ calculated for $C_{21}H_{25}N_1O_7S_1$: 436.14, found 436.14.

Example 379: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-[(trifluoromethyl]phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: In dry equipment under nitrogen, sodium hydride (60% oil dispersion) (11. g, 0.275 mol) was added to a solution of 4-[4-(trifluoromethyl)phenoxy]-phenol (50.0 g, 0.197 mol) in dry dimethylformamide (150 mL) at zero degrees Celsius. After fifteen minutes, a solution of dimethylthiocarbamoyl chloride (32.0 g, 0.259 mol) in dry dimethylformamide (100 mL) was added. The reaction was stirred at ambient temperature for sixteen hours. The reaction was poured onto 10% hydrochloric acid solution (1 L). Vacuum filtration of the resulting precipitate provided the thiono compound as a white solid (67.0 g, 100%).

Part B: The thiono compound from part A (70 g, 0.2 mol) was heated to three hundred seventeen degrees Celsius for thirty minutes behind a safety shield. The reaction exothermed to three hundred thirty degrees Celsius. The heat was removed and the reaction came to ambient temperature to yield the thiocarbamate as a brown solid (70 g, 100%).

Part C: To a solution of the thiocarbamate from part B (65.0 g, 0.19 mol) in methanol (510 mL) with a subsurface nitrogen stream was added 2.5N sodium hydroxide solution (160 mL, 0.4 mol). The slurry was stirred at seventy four degrees Celsius for two hours. The reaction was cooled and the methanol removed *in vacuo*. The residue was diluted

with water (100 mL) and extracted with diethyl ether four times. A subsurface stream of nitrogen was added to the aqueous solution and sodium chloroacetate (22.2 g, 0.19 mol) was added. The reaction was stirred an ambient temperature and after thirty minutes the nitrogen stream was removed. After twelve hours, the solution was cooled and 6N hydrochloric acid was added until the pH=1. The slurry was extracted with ethyl acetate four times. The combined ethyl acetate extracts were washed with 0.1N hydrochloric acid, water, brine, dried over Na_2SO_4, filtered and dried *in vacuo* to give the thioacetic acid as a tan solid (61.0 g, 98%).

Part D: To a solution of the thioacetic acid from part C (54.45g, 0.166 mol) in tetrahydrofuran (370 mL) was added water (45 mL) and Oxone® (306 g, 0.498 mol) at twenty degrees Celsius. An exotherm to forty two degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with tetrahydrofuran and then water (250 mL) was added to the filtrate. The filtrate was concentrated *in vacuo*. The slurry was extracted with ethyl acetate four times. The combined extracts were washed with water three times, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the sulfone as a beige solid (60.0 g, 100%).

Part E: A solution of the sulfone from part D (119.52 g, 0.332 mol) in methanol (660 mL) and 4N hydrochloric acid in dioxane solution (20 mL) was stirred at ambient temperature for twelve hours. The reaction was heated to a boil and cooled slowly to ambient temperature. The resulting crystals were

filtered, washed well with cold methanol, and dried to give the methyl ester as a white solid (89.4 g, 72%).

Part F: To a solution of the methyl ester from part E (64.5 g, 0.180 mol) in dimethylacetamide (360 mL) was added potassium carbonate (66.8 g, 0.48 mol), bis-(2-bromoethyl)ether (40 mL, 0.305 mol), 4-dimethylaminopyridine (1.1 g, 9 mmol), and tetrabutylammonium bromide (2.9 g, 9 mmol). The reaction was stirred overnight at ambient temperature. The reaction was slowly poured into 1N HCl (500 mL). The resulting precipitate was filtered, washed with water, then hexanes. The solid was recrystallized from methanol to give the pyran compound as a white solid (62.8 g, 79%). MS (ES+) $M+NH_4^+$ calculated for $C_{20}H_{19}O_{56}S_1F_3$: 462.12, found 462.12.

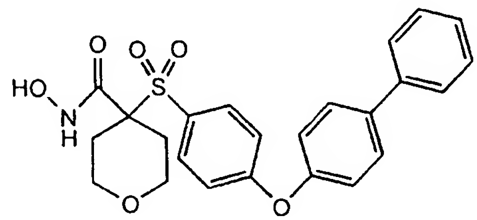
Part G: In dry equipment under nitrogen, the pyran compound from part F (64.0 g, 0.144 mol) was dissolved in dry tetrahydrofuran (250 mL) and a solution of potassium trimethylsilonate (55.9 g, 0.432 mol) in dry tetrahydrofuran (40 mL) was added at ambient temperature. After two hours, water (200 mL) was added and the solution concentrated *in vacuo*. The slurry was extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was heated in diethyl ether, the resulting solid filtered and dried to give the carboxylic acid as a white

solid (56.3 g, 91%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{19}H_{17}O_6 S_1F_3$: 448.10, found 448.10.

Part H: In dry equipment under nitrogen, the carboxylic acid from part G (49.0 g, 0.114 mol) was dissolved in dry dimethylformamide (280 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (18.5 g, 0.137 mol), N-methylmorpholine (37.5 mL, 0.342 mol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (41.3 g, 0.353 mol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 30.6 g, 0.160 mol). After four hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the THP hydroxamate as a white foam (62.6 g, 100%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{24}H_{26}NO_7S_1F_3$: 547.17, found 547.17.

Part I: To a solution of the THP hydroxamate from part H (58.5 g, 0.11 mol) in 1,4-dioxane (280 mL) was added 4N HCl dioxane solution (280 mL) and methanol (280 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (42.79 g, 87%) HRMS (ES+) $M+NH_4^+$ calculated for $C_{19}H_{18}NO_6S_1F_3$: 463, found 463.

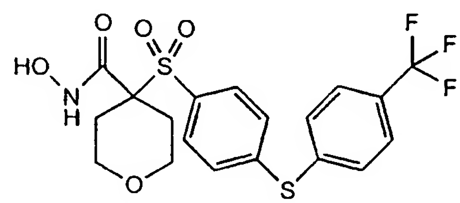
Example 380: Preparation of 4-[[4-([1,1'-biphenyl]-4-yloxy]phenyl) sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (8 mL) was added 4-phenylphenol (Aldrich, 1.3 g, 7.8 mmol) followed by cesium carbonate (6.8 g, 20.8 mmol). The reaction was heated at ninety-five degrees Celsius for five hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (5.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected biphenyl product in solution.

Part B: To the collected THP-protected diphenyl product from A in acetonitrile/ water (50 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eithteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (2.0 g, 83%). MS (FAB) M^+H calculated for $C_{24}H_{23}NO_6S$: 454, found 454.

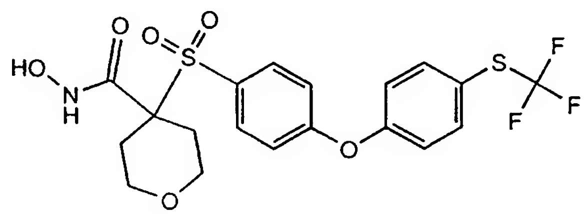
Example 381: Preparation of tetrahydro-N-hydroxy-4-[[4-[[4-(trifluoromethyl)phenyl]thio]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6 mL) was added 4-trifluoromethylthiophenol (Maybridge, 2.0 g, 11.2 mmol), followed by potassium carbonate (2.9 g, 20.8 mmol). The reaction was heated at sixty-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (6.5 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected trifluoromethyl product in solution.

Part B: To the solution of the crude THP-protected trifluoromethyl product from in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a tan solid (0.75 g, 31 %). MS (FAB) $M^{+}H$ calculated for $C_{19}H_{18}F_3NO_5S_2$: 462, found 462.

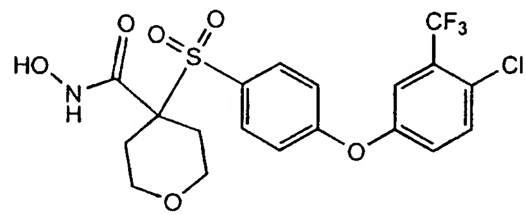
Example 382: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-[(trifluoromethyl)thio]phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6 mL) was added 4-(trifluoromethylthio)thiophenol (Aldrich, 1.5 g, 7.8 mmol) followed by cesium carbonate (6.8 g, 20.8 mmol). After adding a catalytic amount of potassium fluoride, the reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (7.2 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected trifluoromethylthio product in solution.

Part B: To the solution of the crude THP-protected trifluoromethylthio product from A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a tan solid (0.60 g, 24 %). MS (FAB) M^-H calculated for $C_{19}H_{18}F_3NO_6S_2$: 476, found 476.

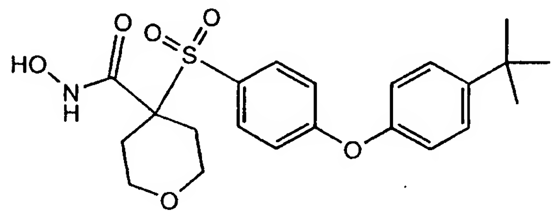
Example 380: Preparation of 4-[[4-[4-chloro-3-(trifluoro-methyl)phenoxy]phenyl] sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6 mL) was added 4-chloro-3-trifluoromethylphenol (Avocado, 1.5 g, 7.8 mmol) followed by cesium carbonate (6.8 g, 20.8 mmol). The reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (7.6 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-protected product from in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (0.92 g, 37 %). MS (FAB) $M^{+}H$ calculated for $C_{19}H_{17}ClF_3NO_6S$: 480, found 480.

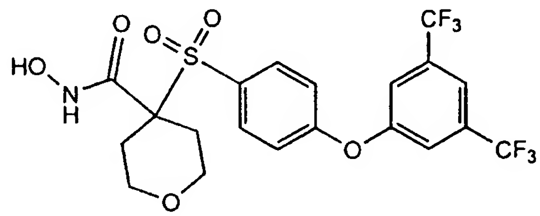
Example 384: Preparation of 4-[[4-[4-(1,1-dimethylethyl)-phenoxy]phenyl] sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (5.0 g, 12.9 mmol) in dimethylacetamide (25 mL) was added 4-t-butylphenol (Avocado, 2.9 g, 19.4 mmol) followed by cesium carbonate (20.4 g, 20.862.5 mmol). The reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (9.4 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-protected product from in acetonitrile/water (60 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (0.28 g, 5 %). MS (FAB) $M^{+}H$ calculated for $C_{22}H_{27}NO_6S$: 434, found 434.

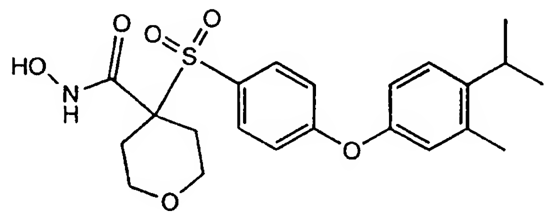
Example 385: Preparation of 4-[[4-[3,5-bis(trifluoromethyl)phenoxy] phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (3.0 g, 7.7 mmol) in dimethylacetamide (15 mL) was added 3,5-ditrifluoromethylphenol (2.9 g, 19.4 mmol) followed by cesium carbonate (20.4 g, 20.862.5 mmol). The reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (14.7 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-protected product from in acetonitrile water (60 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (1.2 g, 31 %). MS (FAB) $M^{+}H$ calculated for $C_{20}H_{17}F_6NO_6S$: 514, found 514.

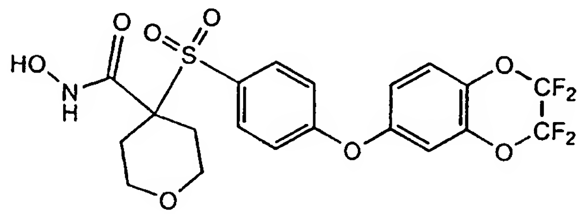
Example 386: Preparation of tetrahydro-N-hydroxy-4-[[4-[3-methyl-4-(1-methylethyl) phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (4.0 g, 10.3 mmol) in dimethylacetamide (20 mL) was added 4-isopropyl-3-methylphenol (Aldrich, 2.3 g,15.5 mmol) followed by cesium carbonate (16.8 g, 51.5 mmol). The reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (18.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-protected product from A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a tan solid (1.8 g, 40 %). MS (FAB) $M^{-}H$ calculated for $C_{22}H_{27}F_3NO_6S$: 432, found 432.

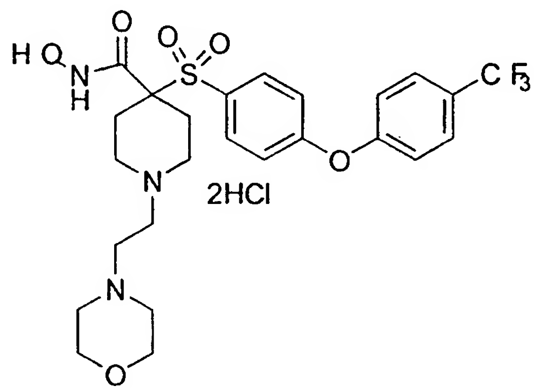
Example 387: Preparation of Tetrahydro-N-hydroxy-4-[[4-[(2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl]oxy]phenyl] sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (5.0 g, 12.9 mmol) in dimethylacetamide (25 mL) was added 2,2,3,3-tetrafluoro-6-hydroxybenzodioxene (Oakwood, 4.3 g, 19.4 mmol) followed by cesium carbonate (21.0 g, 64.5 mmol). The reaction was heated at ninety-five degrees Celsius for five hours. Stripping the dimethylacetamide *in vacuo* afforded a brown solid (11.3 g, quantitative) Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the collected THP-protected product from A in acetonitrile/water (50 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (3.5 g, 54%). MS (FAB) M^-H calculated for $C_{20}H_{17}F_4NO_8S$: 506, found 506.

Example 388: Preparation of N-hydroxy-1-[2-(4-morpholinyl)-ethyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-phenyl] sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: To a suspension of 4-bromopiperidine hydrobromide (107.0 g, 0.436 mol) in tetrahydrofuran (1 L) was slowly added triethylamine (122 mL, 0.872 mol) followed by di-tert-butyl dicarbonate (100 g, 0.458 mol), which was added in several portions. The resulting mixture was stirred at ambient temperature for 22 hours then filtered and concentrated *in vacuo*. The solids were washed with hexanes and then collected by filtration to give the Boc-piperidine compound as an amber oil (124 g, >100 %).

Part B: To a solution of 4-fluorophenol (50.0 g, 0.390 mol) in acetone (400 mL), degassed with N_2, was added Cs_2CO_3 (159 g, 0.488 mol). After degassing the resulting mixture with N_2 for 5 minutes, the Boc-piperidine compound of part A (85.9 g, 0.325 mol) was added. The resulting mixture was stirred at ambient temperature for 18 hours and then filtered through a

pad of Celite®, washing with acetone. The filtrate was concentrated *in vacuo* to provide the sulfide as a tan residue (98.5 g, 97%).

Part C: To a solution of the sulfide of part B (8.00 g, 25.7 mmol) in dichloromethane (90 mL) and methanol (15 mL) was added monoperoxyphthalic acid magnesium salt hexahydrate (19.1 g, 38.6 mmol) in two portions. The resulting mixture was stirred at ambient temperature for 1.5 hours and then filtered. The filtrate was washed with saturated $NaHCO_3$ and then with saturated NaCl. The combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated *in vacuo*. The resulting solids were washed with hexanes then dissolved in dichloromethane and filtered through a pad of Celite®, washing with dichloromethane. The filtrate was concentrated *in vacuo* and recrystallization from ethyl acetate provided the sulfone as a white crystalline solid (4.45 g, 50%).

Part D: To a solution of sulfone of part C (7.00 g, 20.4 mmol) in N,N-dimethylformamide (40 mL) was added Cs_2CO_3 (19.9 g, 61.2 mmol) and α,α,α-trifluoro-p-cresol (3.97 g, 24.5 mmol). The resulting mixture was heated at eighty degrees Celsius for 16 hours. After cooling to ambient temperature the reaction mixture was concentrated *in vacuo*. The resulting residue was treated with H_2O and the solids were collected by filtration. The solids were then washed with hexanes then methanol to provide the biaryl ether as a tan solid (8.60 g, 87%).

Part E: To a solution of the biaryl ether of part D (8.59 g, 17.7 mmol) in tetrahydrofuran (100 mL), cooled to zero degrees Celsius, was slowly added lithium bis(trimethylsilyl)amide (22.0 mL, 1.0M in tetrahydrofuran, 22.0 mmol), at such a rate that the temperature of the reaction never exceeded one degree Celsius. The resulting mixture was stirred at zero degrees Celsius for 1 hour then a solution of methyl chloroformate (2.05 mL, 26.6 mmol) in tetrahydrofuran (5.0 mL) was slowly added, at such a rate that the temperature of the reaction mixture never exceeded four degrees Celsius. After the addition was complete, the mixture was slowly permitted to warm to ambient temperature. Saturated NH_4Cl (50 mL) was added and the tetrahydrofuran was removed *in vacuo*. Water (50 mL) was added to the residue which was then extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Recrystallization from methanol provided the methyl ester as a pale yellow crystalline solid (7.66 g, 80%).

Part F: To a solution of the methyl ester of part E (7.66 g, 14.1 mmol) in dioxane (30 mL) and methanol (10 mL) was added a solution of 4N HCl in dioxane (10 mL, 40 mmol). After stirring at ambient temperature for 2 hours additional 4N HCl in dioxane (10 mL, 40 mmol) was added. After stirring at ambient temperature for 2.5 hours, the reaction mixture was concentrated *in vacuo* to provide the amine as an off-white solid (6.80 g, >100%).

Part G: To a suspension of the amine of part F (3.00 g, 6.25 mmol) in acetonitrile (20 mL) was added K_2CO_3 (3.46 g, 25.0 mmol), 4-(2-chloroethyl)morpholine

hydrochloride (1.22 g, 6.56 mmol) and a catalytic amount of NaI. The resulting mixture was heated at reflux for 22 hours. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the morpholinyl ethyl amine as a tan solid (3.45 g, >100%).

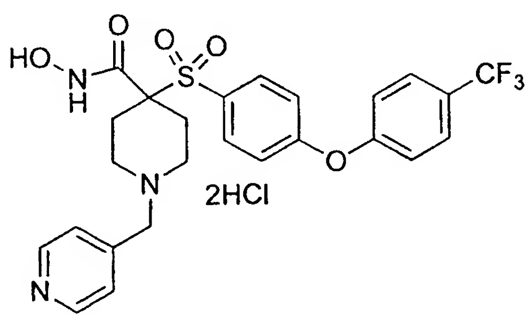
Part H: To a solution of the morpholinyl ethyl amine of part G (3.45 g, 6.25 mmol) in tetrahydrofuran (60 mL) was added potassium trimethylsilanolate (1.60 g, 12.50 mmol). After stirring at ambient temperature for 25 hours, H_2O was added. The reaction mixture was then neutralized (pH 7) with 1N HCl. The tetrahydrofuran was removed *in vacuo* and the resulting precipitate was collected by filtration and washed with diethyl ether to provide the amino acid as an off-white solid (2.87 g, 85%).

Part I: To a suspension of the amino acid of part H (2.87 g, 5.29 mmol) in dichloromethane (25 mL) was added N-methylmorpholine (1.74 mL, 15.9 mmol), O-(tetrahydropuranyl) hydroxylamine (0.682 g, 5.82 mmol) and PyBroP® (2.96 g, 6.35 mmol). After stirring at ambient temperature for 19 hours additional N-methylmorpholine (0.872 mL, 7.94 mmol), O-(tetrahydropuranyl) hydroxylamine (0.310 g, 2.65 mmol) and PyBroP® (1.48 g, 3.17 mmol) were added. The resulting mixture was stirred at ambient temperature for 3 hours and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and H_2O. The organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, methanol/chloroform) provided the

protected hydroxamate as an off-white solid (2.62 g, 77%).

Part J: To a solution of the protected hydroxamate of part I (2.62 g, 4.08 mmol) in dioxane (9 mL) and methanol (3 mL) was added a solution of 4N HCl in dioxane (10 mL, 40.0 mmol). The resulting mixture was stirred at ambient temperature for 2 hours and then diethyl ether (20 mL) was added. The resulting solids were collected by filtration to give the title compound as an off-white solid (2.31 g, 90%). MS MH^+ calculated for $C_{25}H_{31}O_6N_3SF_3$: 558, found 558.

Example 389: Preparation of N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: To a suspension of the amine of part F, Example 388 (1.50 g, 3.13 mmol) in acetonitrile (10 mL) were added K_2CO_3 (1.73 g, 12.5 mmol) and 4-picolyl chloride hydrochloride (0.565 g, 3.44 mmol). After stirring at reflux for 21.5 hours, the reaction mixture was filtered through a pad of Celite®,

washing with ethyl acetate. The filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the picolyl amine as a clear gum (1.44 g, 86%).

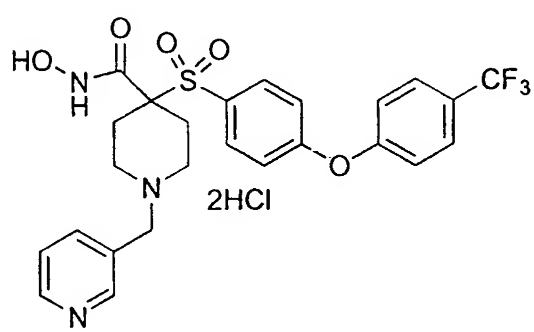
Part B: To a solution of the picolyl amine of part A (1.44 g, 2.69 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.690 g, 5.38 mmol). The resulting mixture was stirred at ambient temperature for 20 hours and then the tetrahydrofuran was removed by blowing N_2 over the reaction mixture. Water (8 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration to provide the amino acid as a white solid (1.31 g, 94%).

Part C: To a suspension of the amino acid of part B (1.31 g, 2.52 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.408 g, 3.02 mmol), N-methylmorpholine (0.831 mL, 7.56 mmol), O-(tetrahydropuranyl) hydroxylamine (0.443 g, 3.78 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.676 g, 3.53 mmol). The resulting mixture was stirred at ambient temperature for 3 days then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetae/hexanes) provided the protected hydroxamate as a white foam (1.24 g, 79%).

Part D: To a solution of the protected hydroxamate of part C (1.24 g, 2.00 mmol) in dioxane (6 mL) and methanol (2 mL) was added a solution of 4N

HCl in dioxane (5.00 mL, 20.0 mmol). After stirring at ambient temperature for 2.5 hours the reaction mixture was concentrated *in vacuo*. The resulting foam was then treated again with a solution of 4N HCl in dioxane (3 mL) for 15 minutes then diethyl ether was added and the resulting precipitate was collected by filtration to provide the title compound as an off-white solid (1.04 g, 85%). MS MH^+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

Example 390: Preparation of N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: To a suspension of the amine of part F, Example 388 (1.00 g, 2.08 mmol) in acetonitrile (10 mL) was added K_2CO_3 (1.15 g, 8.33 mmol) and 3-picolyl chloride hydrochloride (0.375 g, 2.29 mmol). After stirring at reflux for 12 hours, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl

acetate/hexanes) provided the picolyl amine as a pale yellow foam (0.740 g, 67%).

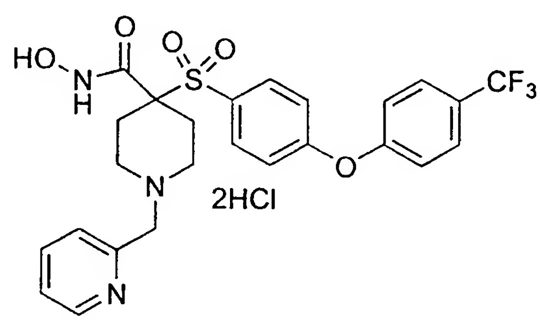
Part B: To a solution of the picolyl amine of part A (0.740 g, 1.38 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.355 g, 2.77 mmol). The resulting mixture was stirred at ambient temperature for 17 hours, then additional potassium trimethylsilanolate (0.044 g, 0.343 mmol) was added and the resulting mixture was stirred at ambient temperature for 2 hours. The tetrahydrofuran was removed by blowing N_2 over the reaction mixture. Water (5 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration and dried by concentration *in vacuo* with acetone to provide the amino acid as an off-white solid (0.700 g, 97%).

Part C: To a suspension of the amino acid of part B (0.700 g, 1.34 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.218 g, 1.61 mmol), N-methylmorpholine (0.442 mL, 4.02 mmol), O-(tetrahydropuranyl) hydroxylamine (0.235 g, 2.01 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.360 g, 1.88 mmol). The resulting mixture was stirred at ambient temperature for 23 hours, then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetae/hexanes) provided the protected hydroxamate as an off-white foam (0.500 g, 60%).

Part D: To a solution of the protected hydroxamate of part C (0.500 g, 0.807 mmol) in

dioxane (1.5 mL) and methanol (0.5 mL) was added a solution of 4N HCl in dioxane (3.0 mL, 12.00 mmol). After stirring at ambient temperature for 2 hours, diethyl ether was added and the resulting precipitate was collected by filtration to provide the title compound as a yellow solid (0.363 g, 74%). MS MH+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

Example 391: Preparation of N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: To a suspension of the amine of part F, Example 388 (1.26 g, 2.63 mmol) in acetonitrile (10 mL) was added K_2CO_3 (1.45 g, 10.5 mmol) and 2-picolyl chloride hydrochloride (0.475 g, 2.89 mmol). After stirring at reflux for 12 hours, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the picolyl amine as an amber oil (1.40 g, 99%).

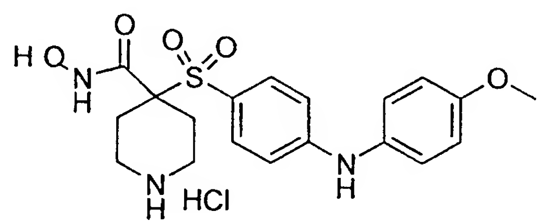
Part B: To a solution of the picolyl amine of part A (1.40 g, 2.62 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.672 g, 5.24 mmol). The resulting mixture was stirred at ambient temperature for 15 hours. The tetrahydrofuran was removed by blowing N_2 over the reaction mixture. H_2O (5 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration and dried by concentration *in vacuo* with acetonitrile to provide the amino acid as an off-white solid (1.07 g, 79%).

Part C: To a suspension of the amino acid of part B (1.07 g, 2.06 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.333 g, 2.47 mmol), N-methylmorpholine (0.679 mL, 6.18 mmol), O-(tetrahydropuranyl) hydroxylamine (0.362 g, 3.09 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.553 g, 2.88 mmol). The resulting mixture was stirred at ambient temperature for 19 hours, then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, methanol/ dichloromethane) provided the protected hydroxamate as a white solid (1.03 g, 81%).

Part D: To a solution of the protected hydroxamate of part C (1.03 g, 1.66 mmol) in dioxane (3.0 mL) and methanol (1.0 mL) was added a solution of 4N HCl in dioxane (3.0 mL, 12.00 mmol). After stirring at ambient temperature for 1.5 hours, diethyl ether was added and the resulting precipitate

was collected by filtration to provide the title compound as a pale pink solid (0.970 g, 96%). MS MH^+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

Example 392: Preparation of N-hydroxy-4-[[4-[(4-methoxyphenyl)amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



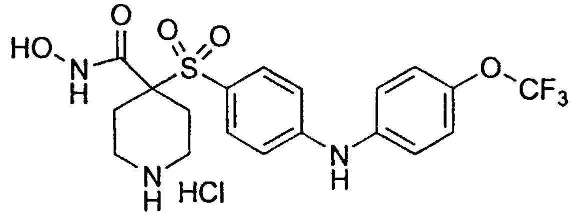
Part A: To the ester of part C, Example 91 (1.00 g, 2.17 mmol) was added Cs_2CO_3 (0.990 g, 3.04 mmol), BINAP (0.061 g, 0.098 mmol), tris(dibenzyldeneacetone)dipallidium (0) (0.060 g, 0.07 mmol), p-anisidine (0.320 g, 2.60 mmol) and toluene (4 mL). The resulting mixture was heated to one hundred degrees Celsius for 22 hours. After cooling to ambient temperature, diethyl ether was added and the mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexane) provided the aniline as an orange foam (0.810 g, 74%).

Part B: To a solution of the aniline of part A (0.780 g, 1.55 mmol) in tetrahydrofuran (4.0 mL) was added potassium trimethylsilanolate (0.238 g, 1.86 mmol). The resulting mixture was stirred at ambient temperature for 17 hours, and then additional potassium trimethylsilanolate (0.020 g, 0.1955mmol)

was added. After stirring at ambient temperature for 24 hours additional potassium trimethylsilanolate (0.040 g, 0.310 mmol) was added. After stirring at ambient temperature for 26 hours, the solvent was removed by blowing N_2 over the mixture. To a suspension of the residue in dichloromethane (10 mL) was added added N-methylmorpholine (0.511 mL, 4.65 mmol), O-(tetrahydropuranyl) hydroxylamine (0.218 g, 1.86 mmol), followed by PyBroP® (1.08 g, 2.33 mmol). The resulting mixture was stirred at ambient temperature for 2 days and then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white solid (0.600 g, 66%).

Part C: To a solution of the protected hydroxamate of part B (0.580 g, 0.984 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (2.5 mL, 10.0 mmol). The resulting mixture was stirred at ambient temperature for 1 hour, then diethyl ether (10 mL) was added. The solids were collected by filtration to give the title compound as a white solid (0.437 g, 100%). MS MH^+ calculated for $C_{19}H_{24}O_5N_3S$: 406, found 406.

Example 393: Preparation of N-hydroxy-4-[[4-[[4-(trifluoromethoxy)phenyl]amino]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the ester of part C, Example 91 (3.27 g, 7.09 mmol) was added Cs_2CO_3 (3.23 g, 9.92 mmol), BINAP (0.066 g, 0.107 mmol), tris(dibenzyldeneacetone)-dipallidium (0) (0.065 g, 0.071 mmol), 4-trifluoro-methoxyaniline (1.15 mL, 8.51 mmol) and toluene (14 mL). The resulting mixture was heated to one hundred degrees Celsius for 22 hours. After cooling to ambient temperature, the mixture was filtered through a pad of Celite®, washing with ethyl acetate, and the filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexane) provided the aniline as a tan solid (3.59 g, 91%).

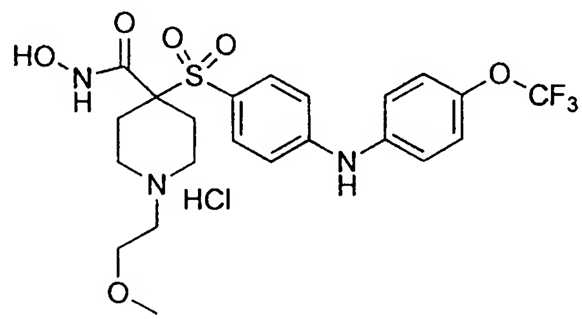
Part B: To a solution of the aniline of part A (1.03 g, 1.84 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.331 g, 2.58 mmol). The resulting mixture was stirred at ambient temperature for 24 hours, and then additional potassium trimethylsilanolate (0.118 g, 0.092 mmol) was added. After stirring at ambient temperature for 24 hours, the solvent was removed by blowing N_2 over the mixture. H_2O was added and the reaction mixture was acidified (pH 3) with 1N HCl. The aqueous reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration

in vacuo provided the acid as a tan solid (1.01 g, 100%).

Part C: To a suspension of the acid of part B (1.00 g, 1.84 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.298 g, 2.21 mmol), N-methylmorpholine (0.607 mL, 5.52 mmol), O-(tetrahydropuranyl) hydroxylamine (0.323 g, 2.76 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.494 g, 2.58 mmol). The resulting mixture was stirred at ambient temperature for 17 hours then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a white solid (0.960 g, 81%).

Part D: To a solution of the protected hydroxamate of part C (0.960 g, 1.49 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (4.0 mL, 16.0 mmol). The resulting mixture was stirred at ambient temperature for 2.5 hours. The solvent was then removed by blowing N_2 over the reaction mixture. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to give the title compound as a pale pink solid (0.716 g, 100%). MS MH^+ calculated for $C_{19}H_{21}O_5N_3SF_3$: 460, found 460.

Example 394: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[4-(trifluoromethoxy)phenyl]amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the aniline of part A, Example 392(2.55 g, 4.57 mmol) in dioxane (9.0 mL) and methanol (3.0 mL) was added a solution of 4N HCl in dioxane (10 mL, 40 mmol). After stirring at ambient temperature for 2 hours, the reaction mixture was concentrated *in vacuo* to provide the amine as a tan solid (2.36 g, >100%).

Part B: To a suspension of the amine of part A (1.50 g, 3.03 mmol) in acetonitrile (12 mL) was added K_2CO_3 (1.26 g, 9.09 mmol) and 2-bromoethyl methyl ether (0.313 mL, 3.33 mmol). After stirring at reflux for 23 hours, Cs_2CO_3 (2.96 g, 9.09 mmol) was added. After 6 hours at reflux, the reaction mixture was filtered through a pad of Celite®, washing with dichloromethane. The filtrate was concentrated *in vacuo*. Chromatography (on silica, methanol/dichloromethane) provided the methoxy ethyl amine as a tan solid (1.13 g, 72%).

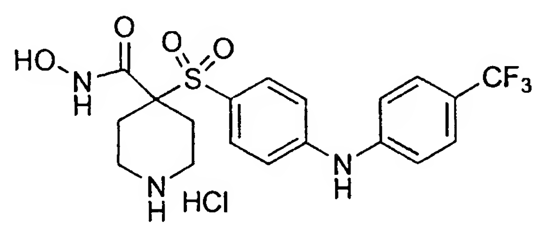
Part C: To a solution of the methoxy ethyl amine of part B (1.13 g, 2.19 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.561 g, 4.38 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, and then additional potassium trimethylsilanolate (0.140 g, 1.09 mmol) was added. After stirring at ambient temperature for 5 hours, the solvent was removed by blowing N_2 over the mixture. Water (8 mL) was added and the reaction mixture was neutralized (pH 7) with 1N HCl. The solids were collected by filtration and dried by concentration *in vacuo* with acetonitrile to provide the amino acid as an off-white solid (0.900 g, 82%).

Part D: To a suspension of the amino acid of part C (0.900 g, 1.79 mmol) in N,N-dimethylformamide (8.0 mL) was added 1-hydroxybenzotriazole (0.290 g, 2.15 mmol), N-methylmorpholine (0.590 mL, 5.37 mmol), O-(tetrahydropuranyl) hydroxylamine (0.315 g, 2.69 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.480 g, 2.51 mmol). The resulting mixture was stirred at ambient temperature for 16 hours then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, methanol/dichloromethane) provided the protected hydroxamate as an off-white solid (0.870 g, 81%).

Part E: To a solution of the protected hydroxamate of part D (0.870 g, 1.45 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (10 mL, 40.0 mmol). The resulting

mixture was stirred at ambient temperature for 2.0 hours. The reaction mixture was concentrated *in vacuo* and then treated again with 4N HCl (3 mL) for 30 minutes. The solvent was then removed by blowing N_2 over the reaction mixture. Diethyl ether (30 mL) was added, and the precipitate was collected by filtration to give the title compound as a pale pink solid (0.771 g, 96%). MS MH^+ calculated for $C_{22}H_{27}O_6N_3SF_3$: 518, found 518.

Example 395: Preparation of N-hydroxy-4-[[4-[[4-(trifluoromethyl)phenyl]amino]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the ester of part C, Example 91 (3.16 g, 6.85 mmol) was added Cs_2CO_3 (3.13 g, 9.59 mmol), BINAP (0.064 g, 0.103 mmol), tris(dibenzyldeneacetone)-dipallidium (0) (0.063 g, 0.069 mmol), α,α,α-trifluoro-methylaniline (1.03 mL, 8.22 mmol) and toluene (14 mL). The resulting mixture was heated to one hundred degrees Celsius for 17 hours. After cooling to ambient temperature, the mixture was filtered through a pad of Celite®, washing with dichloromethane, and the filtrate was concentrated *in vacuo*. Chromatography (on silica,

ethyl acetate/hexane) provided the aniline as a pale orange foam (3.08 g, 83%).

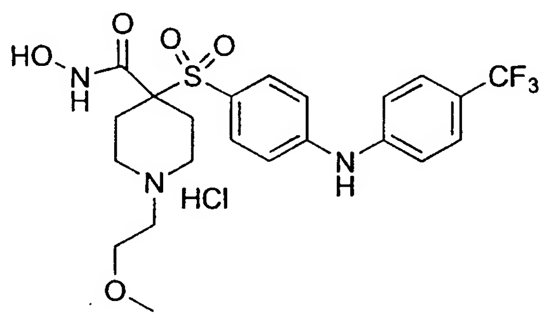
Part B: To a solution of the aniline of part A (1.00 g, 1.84 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.473 g, 3.69 mmol). The resulting mixture was stirred at ambient temperature for 25 hours then the solvent was removed by blowing N_2 over the mixture. Water was added, and the reaction mixture was acidified (pH 3) with 1N HCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the acid as an orange foam (1.00 g, >100%).

Part C: To a suspension of the acid of part B (0.972 g, 1.84 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.298 g, 2.21 mmol), N-methylmorpholine (0.607 mL, 5.52 mmol), O-(tetrahydropuranyl) hydroxylamine (0.323 g, 2.76 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.494 g, 2.58 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a white solid (0.970 g, 84%).

Part D: To a solution of the protected hydroxamate of part C (0.950 g, 1.51 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (4.0 mL, 16.0 mmol). The resulting

mixture was stirred at ambient temperature for 1.5 hours. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to give the title compound as a white solid (0.630 g, 87%). MS MH^+ calculated for $C_{19}H_{21}O_4N_3SF_3$: 444, found 444.

Example 396: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[4-(trifluoromethyl)phenyl]amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the aniline of part A, Example 395 (2.07 g, 3.82 mmol) in dioxane (9.0 mL) and methanol (3.0 mL) was added a solution of 4N HCl in dioxane (10 mL, 40 mmol). After stirring at ambient temperature for 2 hours, the reaction mixture was concentrated *in vacuo* to provide the amine as a yellow solid (1.89 g, >100%).

Part B: To a suspension of the amine of part A (1.83 g, 3.82 mmol) in acetonitrile (20 mL) was added K_2CO_3 (1.58 g, 11.46 mmol) and 2-bromoethyl methyl ether (0.395 mL, 4.20 mmol). After stirring at reflux for 18 hours, the reaction mixture was

filtered through a pad of Celite®, washing with dichloromethane and the filtrate was concentrated *in vacuo*. Chromatography (on silica, methanol/dichloromethane) provided the methoxy ethyl amine as an off-white solid (1.58 g, 83%).

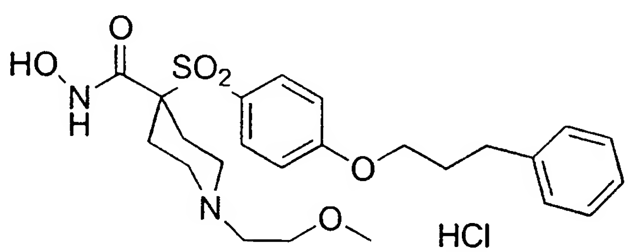
Part C: To a solution of the methoxy ethyl amine of part B (1.58 g, 3.15 mmol) in tetrahydrofuran (30 mL) was added potassium trimethylsilanolate (0.810 g, 6.31 mmol). The resulting mixture was stirred at ambient temperature for 3 days, and then the solvent was removed by blowing N_2 over the mixture. Water (10 mL) was added and the reaction mixture was neutralized (pH 7) with 1N HCl. The solids were collected by filtration and dried by concentration *in vacuo* with acetonitrile to provide the amino acid as a pink solid (1.32 g, 86%).

Part D: To a suspension of the amino acid of part C (1.32 g, 2.71 mmol) in N,N-dimethylformamide (12 mL) was added 1-hydroxybenzotriazole (0.439 g, 3.25 mmol), N-methylmorpholine (0.894 mL, 8.13 mmol), O-(tetrahydropuranyl) hydroxylamine (0.476 g, 4.07 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.727 g, 3.79 mmol). The resulting mixture was stirred at ambient temperature for 20 hours, then concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, methanol/ethyl acetate) provided the protected hydroxamate as an off-white solid (1.39 g, 88%).

Part E: To a solution of the protected hydroxamate of part D (1.40 g, 2.39 mmol) in dioxane

(3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (5.98 mL, 23.9 mmol). The resulting mixture was stirred at ambient temperature for 2.5 hours. The reaction mixture was concentrated almost to dryness, by blowing N_2 over the reaction mixture. Diethyl ether (25 mL) was added and the precipitate was collected by filtration. The resulting solid was dissolved in methanol (1 mL) and treated with 4N HCl in dioxane (1.5 mL). After stirring at ambient temperature for 1.5 hours, the reaction mixture was slowly added to diethyl ether (50 mL). The resulting precipitate was collected by filtration to give the title compound as an off-white solid (1.08 g, 84%). MS MH^+ calculated for $C_{22}H_{27}O_5N_3SF_3$: 502, found 502.

Example 397: Preparation of ethyl 1-(2-methoxyethyl)-3-phenylpropoxy)phenyl]sulfonyl]-4-piperidinecarboxylate



Part A: A mixture of the methoxyethyl amine, ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.5 g, 4.0 mmol), 3-phenyl-1-propanol (2.2 mL, 16 mmol), and K_2CO_3 (2.2 g, 16 mmol) in DMAC (6 mL) was heated at 125 degrees Celsius for 1 day and at 135 degrees Celsius for 3 days. After the mixture was

concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated *in vacuo* to give a crude oil. The oil was purified by flash chromatography (20:80 hexane/ethyl acetate) to afford the ether as a brown oil (1.35 g, 67%).

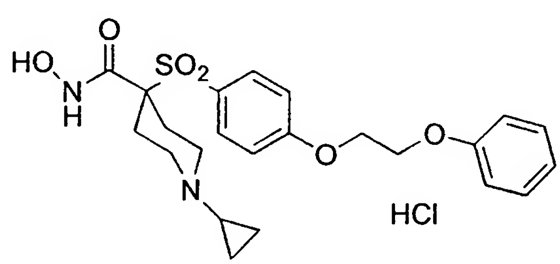
Part B: A mixture of the ether of part A (1.3 g, 2.7 mmol) and a 50% NaOH aqueous solution (2.1 g, 27 mmol) in THF (23 mL), EtOH (23 mL), and H_2O (12 mL) was heated at 60 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated *in vacuo* and triturated with diethyl ether to give a solid. The solid was dissolved in water, cooled with an ice bath, acidified with concentrated hydrochloric acid. The precipitate was isolated by filtration, washed with cold water, and dried at ambient temperature in a vacuum oven for 3 days to afford the crude acid.

A mixture of the above crude acid (1.1 g), N-hydroxybenzotriazole (0.36 g, 2.7 mmol), 4-methylmorpholine (0.74 mL, 6.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.39 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.60 g, 3.1 mmol) in DMF (11 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18 hours. The mixture was concentrated *in vacuo*, and dissolved into a solution of saturated $NaHCO_3$ (90 mL), ethyl acetate (25 mL), and a few drops of 2N NaOH. The aqueous layer was extracted with additional ethyl acetate. The combined ethyl acetate layers were washed with saturated $NaHCO_3$ solution, water, and brine. After

drying over magnesium sulfate, the filtrate was concentrated *in vacuo* to give a dark yellow oil. The oil was purified by flash chromatography (40:60 acetonitrile/toluene) to afford the protected hydroxamate as a yellow oil (0.32 g, 25%): MS MH+ calcd. for $C_{29}H_{40}N_2O_7S$ 561, found 561.

Part C: To a solution of the protected hydroxamate of part 2B (0.28 g, 0.50 mmol) in methanol (4.0 mL) was added acetyl chloride (0.11 mL, 1.5 mmol) and the solution was stirred at ambient temperature under a nitrogen atmosphere for 2.5 hours. The solution was diluted with diethyl ether and concentrated. The solid was triturated with diethyl ether and dried at 40 degrees Celsius in a vacuum oven to give the title compound as an off white solid (0.15 g, 20%): MS MH+ calcd. for $C_{24}H_{32}N_2O_6S$ 477, found 477.

Example 398: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-(2-phenoxyethoxy)phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, part E (14.36 g, 40 mmol) in methanol (50 mL) was added acetic acid (24.5 g, 400 mmol), a portion (about 2 g) of 4-Angstrom molecular sieves,

(1-ethoxycyclopropyl)-oxytrimethyl silane (25.8 mL, 148 mmol) and sodium cyanoborohydride (7.05 g, 112 mmol). The solution was heated at reflux for 8 hours. The precipitated solids were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid was filtered, washed with H_2O/diethyl ether to give the desired cyclopropyl amine {ethyl-4-[(4-fluorophenyl-sulfonyl)]-1-cyclopropyl-4-piperidinecarboxylate} as a white solid (11.83 g, 81.5%). MS MH^+ calculated for $C_{17}H_{22}NO_4SF$: 356, found : 356.

Part B: A solution of the cyclopropyl amine of Part A (2.0 g, 5.6 mmol), ethylene glycol phenyl ether (2.8 mL, 23 mmol), and cesium carbonate (7.3 g, 23 mmol) in DMAC (10 mL) was heat at 125-135 degrees Celsius for 18 hours under an atmosphere of nitrogen. The mixture was concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water and brine, dried over magnesium sulfate, concentrated *in vacuo*, dissolved in diethyl ether, precipitated as the hydrochloride salt, and dried at 40 degrees Celsius in a vacuum oven. The solid was dissolved into a mixture of water, acetonitrile, and ethanol and then the pH was adjusted to 12 with 1N NaOH solution. The mixture was concentrated *in vacuo* to remove ethanol and acetonitrile. The solid was isolated by filtration, washed with water, and dried at 50 degrees Celsius in a vacuum oven to afford the ether as a white solid (1.8 g, 68%): MS+ calcd. for

$C_{25}H_{31}NO_6S$ 474, found 474. Anal. calcd. for $C_{25}H_{31}NO_6S$: C, 63.40; H, 6.60; N, 2.96; S, 6.77. Found: C, 63.35; H, 6.59; N, 2.99; S, 6.61.

Part C: A mixture of the ether of part B (1.8 g, 3.7 mmol) and a 50% NaOH aqueous solution (3.0 g, 37 mmol) in THF (32 mL), EtOH (32 mL), and H_2O (16 mL) was heated at 60 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated *in vacuo* and triturated with diethyl ether to give a solid. The tan solid was dissolved into a mixture of water, ethanol, and THF, precipitated by adjusting the pH to 3 with concentrated hydrochloric acid, concentrated *in vacuo*, triturated with water, and dried at 50 degrees Celsius in a vacuum oven to give a crude white solid acid (2.3 g).

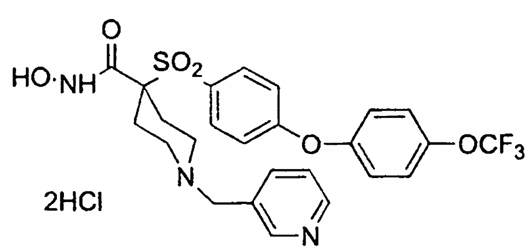
A mixture of the crude white solid acid (2.3 g), N-hydroxybenzotriazole (1.9 g, 14 mmol), 4-methylmorpholine (1.6 mL, 14 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.1 g, 9.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.7 g, 14 mmol) in DMF (90 mL) was stirred at ambient temperature under a nitrogen atmosphere for 2 days. The mixture was concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate. The organic layer was washed with 1N NaOH solution, water, and brine, dried over magnesium sulfate, concentrated *in vacuo*, and purification by flash chromatography (20:80 to 40:60 ethyl acetate/toluene) to afford the protected hydroxamate as a white solid: (0.43 g, 21%): MS MH+ calcd. for $C_{28}H_{36}N_2O_7S$ 545, found 545. Anal. calcd. for

$C_{28}H_{36}N_2O_7S$: C, 61.74; H, 6.66; N, 5.14; S, 5.89. Found: C, 61.72; H, 6.75; N, 5.06; S, 5.91.

Additional compound was isolated by acidifying the aqueous layer to pH of 3, collecting the solid by filtration, and drying to give a white solid (0.80 g).

Part D: To an ambient temperature solution of acetyl chloride (0.31 mL, 4.4 mmol) in methanol (11 mL) under a nitrogen atmosphere was added the protected hydroxamate of part C (0.80 g, 1.5 mmol). After stirring for 2.5 hours, the precipitate was collected by filtration, washed with diethyl ether, and dried at 45 degrees Celsius in a vacuum oven to afford the title compound as a white solid (0.58 g, 79%): MS MH+ calcd. for $C_{23}H_{28}N_2O_6S$ 461, found 461. Anal. calcd. for $C_{23}H_{28}N_2O_6S \cdot 1.5HCl$: C, 53.62; H, 5.77; N, 5.44; S, 6.22. Found: C, 53.47; H, 5.79; N, 5.41; S, 6.16.

Example 399: Preparation of hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: A solution of the amine hydrochloride salt of the product of Example 410(2.4 g, 4.6 mmol), 3-picolyl chloride (1.5 g, 8.8 mmol), and potassium carbonate (4.3 g, 31 mmol) in DMF (12) was heated at 50 degrees Celsius for 1 day under an atmosphere of nitrogen. The mixture was concentrated *in vacuo*, dissolved into water, and extracted with ethyl acetate. The organic layers were washed with water and brine, dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by flash chromatography (50:50 ethyl acetate/hexane) to afford the 3-picolyl amine as an amber oil (1.6 g, 60%): MS MH+ calcd. for $C_{27}H_{27}N_2O_6SF_3$ 565, found 565. Anal. calcd. for $C_{27}H_{27}N_2O_6SF_3$: C, 57.44; H, 4.82; N, 4.96; S, 5.68. Found: C, 57.49; H, 5.10; N, 4.69; S, 5.67

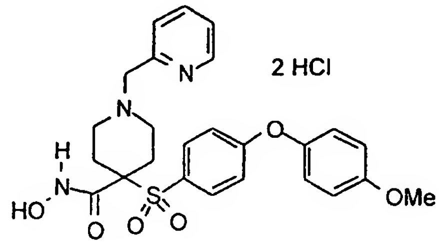
Part B: A mixture of the 3-picolyl amine of part 4A (1.5 g, 2.6 mmol) and a 50% NaOH aqueous solution (2.1 g, 26 mmol) in THF (22 mL), EtOH (22 mL), and H_2O (11 mL) was heated at 65 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated *in vacuo* and triturated with diethyl ether to give a solid. The tan solid was dissolved into water and the pH was adjusted to 1 with concentrated hydrochloric acid. The mixture was concentrated *in vacuo*, and dried in a 45 degrees Celsius vacuum oven to afford the crude white solid acid (2.5 g): MS MH+ calcd. for $C_{25}H_{23}N_2O_6SF_3$ 537, found 537.

Part C: A mixture of the crude white acid of part B (2.5 g), N-hydroxybenzotriazole (1.0 g, 7.7 mmol), 4-methylmorpholine (0.64 mL, 7.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.60 g, 5.1

mmol), and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 7.7 mmol) in DMF (40 mL) was stirred at ambient temperature under a nitrogen atmosphere for 5 days. The mixture was concentrated *in vacuo*, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash chromatography (5:95 methanol/chloroform) to afford the protected hydroxamate as a white foam (1.1 g, 66%): MS MH+ calcd. for $C_{30}H_{32}N_3O_7SF_3$ 636, found 636.

Part D: An ambient temperature solution of the protected hydroxamate of part C (1.0 g, 1.6 mmol) and acetyl chloride (0.34 mL, 4.7 mmol) in methanol (11 mL) under a nitrogen atmosphere was stirring for 2.5 hours, and then poured into diethyl ether. The solid was isolated by filtration and dried at 46 degrees Celsius in a vacuum oven to afford the title compound as a white solid (0.85 g, 87%): Anal. calcd. for $C_{25}H_{24}N_3O_6SF_3 \cdot 2.2HCl$: C, 47.53; H, 4.18; N, 6.65; S, 5.08. Found: C, 47.27; H, 4.34; N, 6.60; S, 5.29. MS MH+ calcd. for $C_{25}H_{24}N_3O_6SF_3$ 552, found 552.

Example 400: Preparation of N-Hydroxy-4-[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-pyridinylmethyl)-4-piperidine-<u>carboxamide, dihydrochloride</u>



Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-4-piperidinecarboxylate hydrochloride (2.02 g, 5.76 mmol) was combined with powdered potassium carbonate (2.48 g, 18 mmol) and N,N-dimethylformamide (12 mL). 2-Picolyl hydrochloride (1.0 g, 6.1 mmol) was added, and the mixture was stirred for twenty-four hours at forty degrees Celsius. The reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (3 X 50mL). The combined organic layers were dried over magnesium sulfate, concentrated, and subjected to chromatography (ethyl acetate) affording the desired pyridine ester as an oil (2.30 g, quantitative).

Part B: The pyridine ethyl ester from Part A (2.30 g, 5.76 mmol) was combined with powdered potassium carbonate (1.29 g, 9 mmol), 4-methoxyphenol (1.12 g, 9.0 mmol), and N,N-dimethylformamide (3 mL), and the mixture was heated at seventy five to eighty degrees C for twenty-four hours. Additional 4-methoxyphenol (300 mg) and potassium carbonate (350 mg) were added, and the mixture was stirred an additional three hours at ninety degrees Celsius. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were dried using magnesium

sulfate, concentrated, and chromatographed, affording the desired ester as an oil (2.85 g, quantitative).

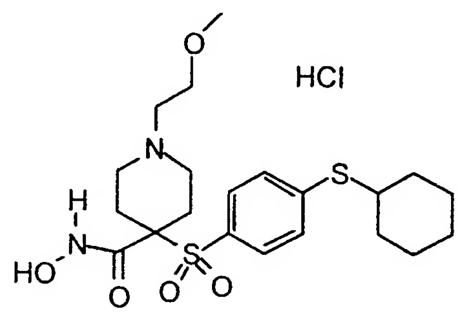
Part C: The ester of part B (2.85 g) was combined with ethanol (18 mL), water (6 mL), and potassium hydroxide (2.24 g, 40 mmol). The mixture was brought to reflux and heated for four and one-half hours. It was cooled to zero degrees Celsius and acidified using concentrated aqueous hydrogen chloride. The solvent was removed, and the resulting solids were dried by azeotroping with acetonitrile. Vacuum was applied until constant weight was achieved.

The crude acid hydrochloride was stirred with N-methylmorpholine (1 mL), 1-hydroxybenzotriazole (0.945 g, 7 mmol), O-tetrahydropyranyl hydroxylamine (0.82 g, 7 mmol), and N,N-dimethyformamide (21 mL). After ten minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.34 g, 7 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (200 mL, then 50 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed (9:1 ethyl acetate: hexane) to afford the desired O-tetrahydropyranyl-protected hydroxamate as a yellow oil (2.82 g, 88%).

Part D: The O- tetrahydropyranyl-protected hydroxamate of part C (2.82 g, 5 mmol) was diluted with methanol (20 mL). Acetyl chloride (2.1 mL, 30 mmol) was added over two minutes. The reaction was stirred for 4 hours at ambient temperature, then concentrated to afford 2.59 g of crude

dihydrochloridesalt, which was recrystallized from ethanol/water, affording 525 mg (18%) of the title hydroxamate in the first crop. MS (EI) MH^+ calculated for $C_{25}H_{27}N_3O_6S$: 498, found 498.

Example 401: Preparation of N-Hydroxy-4-[4-(4-cyclohexylthio)phenyl]sulfonyl]-1-(2-methoxyethyl)-4-piperidine-carboxamide, hydrochloride



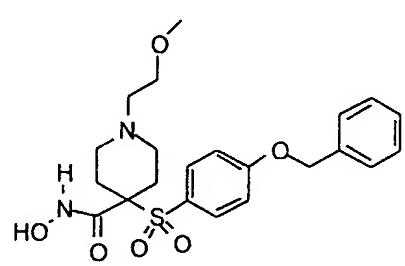
Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (5.5 g, 14 mmol) was combined with powdered potassium carbonate (2.76 g , 20 mmol), N, N-dimethylformamide (7 mL), and cyclohexyl mercaptan (2.4 mL, 20 mmol) and was stirred at ambient temperature for two days. The temperature was raised to forty-five to fifty degrees Celsius and stirring was continued another 24 hours. Additional quantities of potassium carbonate (1.0 g) and cyclohexyl mercaptan (1.0 mL) were introduced and the reaction was heated sixteen additional hours. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (100 mL, then 25 mL). The combined organic layers were dried, concentrated,

and chromatographed (ethyl acetate) affording the desired sulfide as a yellow oil (3.59 mL, 53%).

Part B: The sulfide from Part A (3.59 gm, 7.4 mmol) was converted to tetrahydropyranyl-protected hydroxamate by saponification followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 2.16 g (54%) of the desired tetrahydropyranyl-protected hydroxamate as an oil.

Part C: The tetrahydropyranyl-protected hydroxamate from part B (2.16 g, 4 mmol) was diluted with methanol (16 mL). Acetyl chloride (1.1 mL, 16 mmol) was added over one minute. The reaction was stirred for four hours, then concentrated and azeotroped with acetonitrile to afford 1.11 g of crude product, which was recrystallized from absolute ethanol to afford in the first crop 804 mg of the title compound (41%). MS (EI) MH^+ calculated for $C_{21}H_{32}N_2O_5S_2$: 457, found 457.

Example 402: Preparation of N-Hydroxyl-1-(2-methoxyethyl)-4-[[(phenylmethoxy)phenyl]-sulfonyl]-4-piperidinecarboxamide



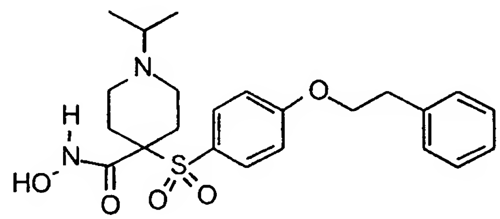
Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.58 g, 4.5 mmol) was combined with powdered potassium carbonate (2.42 g , 18 mmol), N,N-dimethylacetamide (5 mL), and benzyl alcohol (1.94 mL, 18 mmol) and was stirred at one hundred forty degrees Celsius for sixteen hours. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (125 mL, then 25 mL). The combined organic layers were dried, concentrated, and chromatographed (ethyl acetate) affording the desired ethyl ester as an oil (1.16 mL, 56%).

Part B : The ethyl ester from part A (1.16 gm, 2.5 mmol) was converted to the tetrahydropyranyl-protected hydroxamate by saponification followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 880 mg (80%) of the tetrahydropyranyl-protected hydroxamate as an oil.

Part C: The tetrahydropyranyl-protected hydroxamate from Part B (880 mg, 2.0 mmol) was diluted with methanol (8 mL). Acetyl chloride (0.68 mL,10 mmol) was added over one minute. The reaction was stirred for three hours, then concentrated and azeotroped with acetonitrile to afford the crude product, which was converted to free base by adding enough saturated aqueous sodium bicarbonate (25 mL) to neutralize the hydrogen chloride, then extracting with ethyl acetate (100 mL, then 50 mL). The organic phase was dried with magnesium sulfate, concentrated, and chromatographed (9:1 dichloromethane:methanol, 1% ammonium hydroxide), affording the title hydroxamate

as a glass, (327 mg, 36%). MS (EI) MH^+ calculated for $C_{22}H_{28}N_2O_6S$: 447, found 447.

Example 403: Preparation of N-hydroxyl-1-(1-methylethyl)-4-[[4-(2-phenylethoxy)-phenyl]sulfonyl]-4-piperidine carboxamide



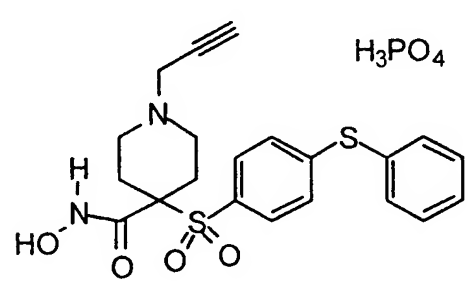
Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-1-(1-methylethyl)-4-piperidinecarboxylate (2.75 g, 7.7 mmol) was combined with powdered potassium carbonate (2.62 g , 19 mmol), N, N-dimethylformamide (10 mL), and 2-phenylethanol (2. mL, 19 mmol) and was stirred at eighty-five degrees Celsius for twenty four hours. Additional potassium carbonate (1.3 g) and 2-phenylethanol were added, and the temperature was raised to one hundred-ten degrees Celsius for forty-eight hours, then one hundred thirty-five degrees Celsius for four hours. The mixture was diluted with water (100 mL), and extracted with ethyl acetate (200 mL, then 25 mL). The combined organic layers were dried, concentrated, and chromatographed (ethyl acetate) affording the desired ethyl ester as an oil (3.19 mL, 90%).

Part B: The ethyl ester from Part A (3.19 gm, 6.9 mmol) was converted to tetrahydropyranyl-protected hydroxamate by saponification followed by

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 2.27 g (64%) of the title compound as an oil.

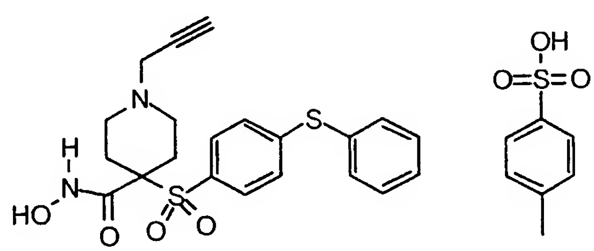
Part C: The tetrahydropyranyl-protected hydroxamate from Part B (2.27 mg, 4.4 mmol) was diluted with methanol (16 mL). Acetyl chloride (0.68 mL,10 mmol) was added over one minute. The reaction was stirred for three hours, then concentrated and azeotroped with acetonitrile to afford the crude product, which was converted to free base by adding enough saturated sodium bicarbonate (25 mL) to neutralize the hydrogen chloride, then extracting with ethyl acetate (100, then 50 mL). The organic phase was dried with magnesium sulfate, concentrated, and chromatographed (9:1 dichloromethane:methanol, 1% ammonium hydroxide), affording the desired hydroxamate as a glass, (819 mg, 42%). MS (EI) MH^+ calculated for $C_{23}H_{30}N_2O_5S$: 449, found 449.

Example 404: Preparation of N-hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, phosphoric acid salt



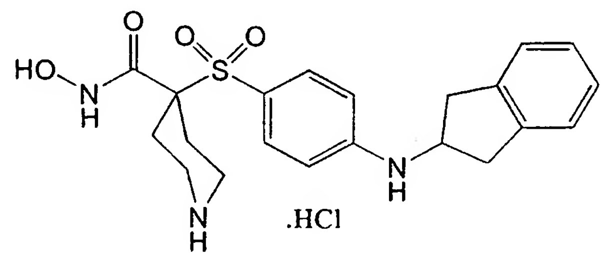
N-Hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide (430 mg, 1.0 mmol) was dissolved in methanol (15 mL). Concentrated phosphoric acid (67 µL) was added, and the solution was then concentrated *in vacuo*. The residue was recrystallized from methanol, isolated by filtration, and then recrystallized a second time from methanol/methyl t-butyl ether affording the title phosphate as a solid (215 mg, 41%). Analytical calculation for $C_{21}H_{22}N_2O_4.H_3PO_4$: C, 47.72; H, 4.77; N, 5.30, found: C, 47.63; H, 5.04; N, 4.82.

Example 405: Preparation of N-hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, p-toluenesulfonic acid salt



N-Hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide (516 mg, 1.0 mmol) was combined with p-toluenesulfonic acid, monohydrate (200 mg, 1.05 mmol), and the mixture was dissolved in methanol (3 mL). After four hours, the resulting white precipitate was collected by filtration affording 488 mg (81%) of the title tosylate salt, which was characterized spectroscopically.

Example 406: Preparation of 4-[[4-[(2,3-dihydro-1H-inden-2-yl)amino]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: A solution of the product of Example 9, Part D (0.979 g, 2.36 mmol), 2-aminoindan hydrochloride (1.00 g, 5.89 mmol), and cesium carbonate (1.92 g, 5.89 mmol) in N,N-dimethylformamide (8 mL) was heated to 95 degrees Celsius for 22 hours. The reaction was then cooled, diluted with ethyl acetate (50 mL), and washed with three times with water and once with brine, then dried over sodium sulfate. Concentration gave a residue that was chromatographed on silica gel. Elution with ethyl acetate/hexane (30/70) afforded the desired 4-aminosulfone derivative (450 mg, 36%). MS (EI) MH^+ calculated for $C_{28}H_{36}N_2O_6S$: 529, found 529. HRMS M+ calculated for $C_{28}H_{36}N_2O_6S$: 528.2294, found 528.2306.

Part B: To a solution of the ethyl ester of part A (450 mg, 0.85 mmol) in ethanol (3 mL), water (2 mL) and tetrahydrofuran (3 mL) was added sodium hydroxide (340 mg, 8.5 mmol), and the solution was heated to 60 degrees Celsius for 26 hours. The

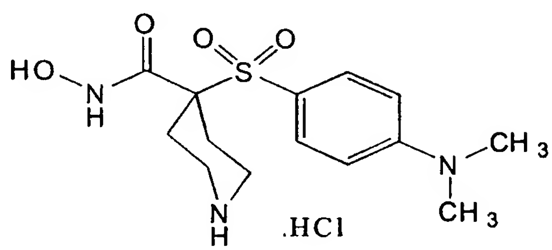
solution was cooled and then diluted with water (10 mL) followed by 10% aqueous hydrochloric acid (3 mL) to bring the pH to 2. The resulting solution was extracted with ethyl acetate. The organic extracts were combined and washed with water and brine and dried over sodium sulfate to afford the desired carboxylic acid as a pale brown foam (376 mg, 88%). Analytical calculation for $C_{26}H_{32}N_2O_6S$: C, 62.38; H, 6.44; N, 5.60; S, 6.40. Found: C, 62.48; H, 6.69; N, 5.42; S, 6.27.

Part C: To a solution of the carboxylic acid of part B (305 mg, 0.609 mmol) in N,N-dimethylformamide (2 mL) was added 4-methylmorpholine (247 mg, 2.44 mmol), N-hydroxybenzotriazole (99 mg, 0.73 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (152 mg, 0.79 mmol) followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (97 mg, 0.82 mmol). After stirring for 2 days at ambient temperature, the solution was concentrated to an oil. Water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over sodium sulfate. Concentration gave a brown foam that was chromatographed on silica gel. Elution with ethyl acetate/hexane (40/60) afforded the protected hydroxamate derivative as a colorless glass (0.38 g, 100%). MS MH^+ calculated for $C_{31}H_{41}N_3O_7S$: 600, found 600.

Part D: To a solution of the protected hydroxamate of part C (350 mg, 0.584 mmol) in methanol (3 mL) and 1,4-dioxane (1.5 mL) was added 4 N HCl/1,4-dioxane (1.5 mL, 6 mmol), and the solution was stirred at ambient temperature for 3 hours.

Concentration gave a residue that was triturated with diethyl ether to afford the title compound as a solid, which was filtered and dried for 40 hours at 51 degrees Celsius (249 mg, 94%). HRMS (ESI) MH^+ calculated for $C_{21}H_{25}N_3O_4S$: 416.1644, found 416.1647.

Example 407: Preparation of 4-[[4-(dimethylamino)-phenyl]sulfonyl]-N-hydroxy-4-piperidine-carboxamide, monohydrochloride



Part A: A solution of the product of Example 9, Part D (0.979 g, 2.36 mmol), 2-aminoindan hydrochloride (1.00 g, 5.89 mmol), and cesium carbonate (1.92 g, 5.89 mmol) in N,N-dimethylformamide (8 mL) was heated to 95 degrees Celsius for 22 hours. The reaction was then cooled, diluted with ethyl acetate (50 mL), and washed with three times with water and once with brine, then dried over sodium sulfate. Concentration gave a residue that was chromatographed on silica gel. Elution with ethyl acetate/hexane (30/70) afforded the 4-N,N-dimethylaminosulfone derivative (590 mg, 57%) alongside the product of example 406. MS (EI) MH^+ calculated for $C_{21}H_{32}N_2O_6S$: 441, found 441. HRMS calculated for $C_{21}H_{32}N_2O_6S$: 440.1981, found 440.1978.

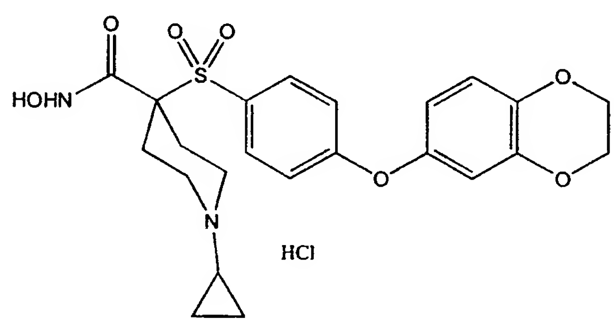
Part B: To a solution of the ethyl ester of part A (580 mg, 1.3 mmol) in ethanol (4 mL), water (3 mL) and tetrahydrofuran (4 mL) was added sodium hydroxide (520 mg, 13 mmol), and the solution was heated to 62 degrees Celsius for 5 hours. The solution was cooled and then diluted with water (5 mL) followed by 10% aqueous hydrochloric acid (5 mL) to acidify to pH=2. The resulting solution was extracted with ethyl acetate. The organic extracts were combined and washed with water and brine and dried over sodium sulfate to afford the desired carboxylic acid as a pale brown foam (520 mg, 97%). MS MH^+ calculated for $C_{19}H_{28}N_2O_6S$: 413, found 413.

Part C: To a solution of the carboxylic acid of part B (500 mg, 1.21 mmol) in N,N-dimethylformamide (4 mL) was added 4-methylmorpholine (490 mg, 4.8 mmol), N-hydroxybenzotriazole (197 mg, 1.45 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (302 mg, 1.57 mmol) followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (192 mg, 1.63 mmol). After stirring for 2 days at ambient temperature, the solution was concentrated to an oil. Water (25 mL) was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over sodium sulfate. Concentration gave a brown oil, which crystallized from a mixture of ethyl acetate, hexane and methylene chloride (1:1:2) to afford the protected hydroxamate derivative as a colorless solid (506 mg, 82%). MS MH^+ calculated for $C_{24}H_{37}N_3O_7S$: 512, found 512.

Part D: To a solution of the protected hydroxamate of part C (477 mg, 0.932 mmol) in

methanol (3 mL) and 1,4-dioxane (3 mL) was added 4 N HCl/1,4-dioxane (2.3 mL, 9.3 mmol), and the solution was stirred at ambient temperature for 3 hours. Concentration gave a residue that was triturated with diethyl ether to afford the title compound as a solid, which was filtered and dried for 40 hours at 51 degrees Celsius (372 mg, 100%). HRMS (ESI) MH^+ calculated for $C_{14}H_{21}N_3O_4S$: 328.1331, found 328.1343.

Example 408: Preparation of 1-cyclopropyl-4-[[4-[(2,3-dihydro-1,4-benzodioxin-6-yl)oxy]phenyl]-sulfonyl]-N-hydroxy-4-piperidine-carboxamide, monohydrochloride



Part A: To a solution of the product of Example 398, Part A (1.36 g, 3.47 mol) in N,N-dimethylformamide (8 mL) was added 6-hydroxybenzo-1,4-dioxane (792 mg, 5.21 mmol) followed by cesium carbonate (2.83 g, 8.69 mmol) and the solution was heated at one hundred degrees Celsius for 20 hours. The solution was partitioned between ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H_2O and saturated NaCl and dried over Na_2SO_4.

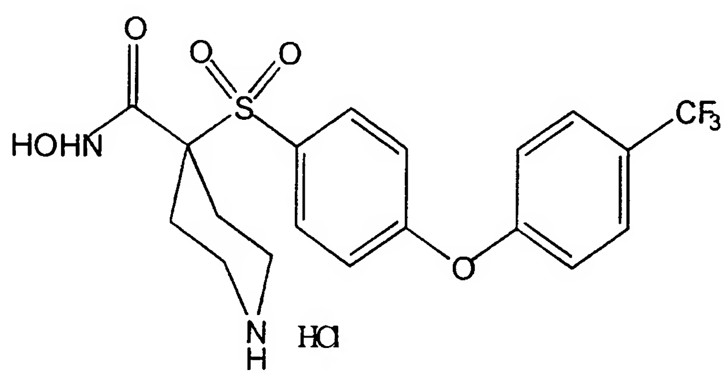
Filtration through a silica pad (ethyl acetate/hexane) provided the phenoxyphenyl compound as an orange oil (1.81 g, quantitative yield). MS(CI) MH^+ calculated for $C_{25}H_{29}NO_7S$: 488, found 488.

Part B: To a solution of the phenoxyphenol compound of part A (1.81 g, <3.47 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.39 g, 34.7 mmol) in H_2O (5 mL). The solution was heated to sixty degrees Celsius for 20 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH = 2 with 10% HCl. The resulting solid was collected by vacuum filtration to provide the acid as a yellow solid (1.23 g, 72%). MS(CI) MH^+ calculated for $C_{23}H_{25}NO_7S$: 460, found 460. HRMS calculated for $C_{23}H_{25}NO_7S$: 460.1430, found 460.1445.

Part C: To a suspension of the acid of part B (1.21 g, 2.46 mmol) in N,N-dimethylformamide (20 mL) was added N-hydroxybenzotriazole (399 mg, 2.95 mmol), 4-methylmorpholine (0.81 mL, 7.38 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (432 mg, 3.69 mmol). After stirring for one hour 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (660 mg, 3.44 mmol) was added and the solution was stirred for 20 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a yellow oil (940 mg, 70 %). MS(CI) MH^+ calculated for $C_{28}H_{34}N_2O_2S$: 559, found 559.

Part D: To a solution of the protected hydroxamate of part C (920 mg, 1.68 mmol) in 1,4-dioxane (15 mL) was added 4N HCl in 1,4-dioxane (10 mL). After stirring at ambient temperature for 2 hours the resulting precipitate was collected by vacuum filtration and washed with ethyl ether to provided the title compound as a white solid (510 mg, 60 %). MS(CI) MH^+ calculated for $C_{23}H_{26}N_2O_7S$: 475, found 475. HRMS calculated for $C_{23}H_{26}NO_7S$: 475.1539, found 475.1553. Analytical calculation for $C_{23}H_{26}N_2O_7S$ •1.15HCl•0.5H_2O: C, 52.57; H, 5.40; N, 5.33; Cl, 7.76. Found: C, 52.62; H, 5.42; N, 5.79; Cl, 7.71.

Example 409: Preparation of N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (1.5 g, 3.61 mmol) in N,N-dimethylformamide (10 mL) was added cesium carbonate (2.94 g, 9.03 mmol) and α,α,α-trifluoro-p-cresol (877 mg, 5.41 mmol). The solution was heated to ninety degrees Celsius for 20 hours. The solution was

partitioned between ethyl acetate and H_2O and the organic layer was washed with saturated NaCl and dried over Na_2SO_4. Filtration through a silica pad (ethyl acetate) provided the diaryl ether as a yellow oil (2.30 g, quantitative yield). MS(CI) MH^+ calculated for $C_{26}H_{30}NO_7SF_3$: 558, found 558.

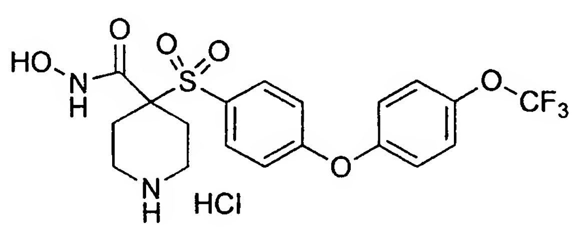
Part B: To a solution of the diaryl ether of part A (2.30 g, <3.61 mmoL) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.44 g, 36.1 mmol) in H_2O (5 mL) and the solution was heated to sixty degrees Celsius for 18 hours. The solution was concentrated and the aqueous residue was acidified to pH = 2 with 10% HCl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the acid as a solid (2.11 g, quantitative yield). MS(CI) MH^+ calculated for $C_{24}H_{26}NO_7SF_3$: 530, found 530.

Part C: To a solution of the acid of part B (2.11 g, <3.61 mmol) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (586 mg, 4.33 mmol), 4-methylmorpholine (1.19 mL, 10.83 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for one hour, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (969 mg, 5.05 mmol) was added and the solution was stirred for 18 hours. The solution was partitioned between ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H_2O and saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a clear, colorless oil (1.40

g, 62 %). MS(CI) MH^+ calculated for $C_{29}H_{35}N_2O_8SF_3$: 629, found 629.

Part D: To a solution of the protected hydroxamate of part C (1.40 g, 2.23 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in 1,4-dioxane (15 mL) and the solution was stirred for 2 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (747 mg, 70 %). HPLC purity: 97.5 %. MS(CI) MH^+ calculated for $C_{19}H_{19}N_2O_5SF_3$: 445, found 445. HRMS calculated for $C_{19}H_{19}N_2O_5SF_3$: 445.1045, found 445.1052. Analytical calculation for $C_{19}H_{19}N_2O_5SF_3 \bullet 0.5H_2O \bullet 1.0HCl$: C, 46.58; H, 4.32; N, 5.72; S, 6.55; Cl, 7.24. Found: C, 46.58; H, 3.82; N, 5.61; S, 6.96; Cl, 7.37.

Example 410: Preparation of N-hydroxy-4-[[4-[(trifluoromethoxy)phenoxy]phenyl] sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (1.5 g, 3.61 mmol) in N,N-dimethylformamide (10 mL) was added cesium carbonate (2.94 g, 9.03 mmol) and 4-(trifluoromethoxy)phenol (0.70 mL, 5.41 mmol). The solution was heated to ninety degrees Celsius for 20 hours. The solution

was partitioned between ethyl acetate and H_2O and the organic layer was washed with saturated NaCl and dried over Na_2SO_4. Filtration through a silica pad (ethyl acetate) provided the phenoxyphenol as a yellow oil (2.11 g, quantitative yield). MS(CI) MNa^+ calculated for $C_{26}H_{30}NO_8SF_3$: 596, found 596.

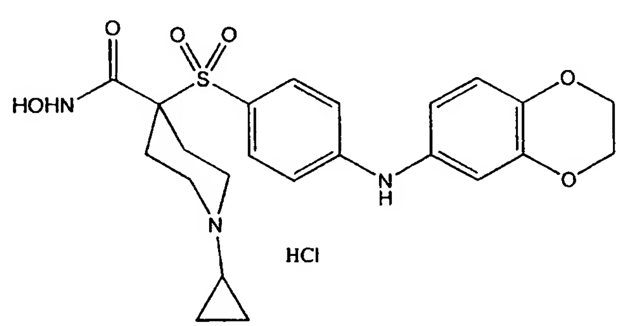
Part B: To a solution of the phenoxyphenol of part A (2.11 g, <3.61 mmoL) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.44 g, 36.1 mmol) in H_2O (5 mL), and the solution was heated to sixty degrees Celsius for 18 hours. The solution was concentrated and the aqueous residue was acidified to pH = 2 with 10% HCl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the acid as a solid (2.2 g, quantitative yield). MS(CI) MH^+ calculated for $C_{24}H_{26}NO_8SF_3$: 546, found 546.

Part C: To a solution of the acid of part B (2.2 g) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (586 mg, 4.33 mmol), 4-methylmorpholine (1.19 mL, 10.83 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for thirty minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (969 mg, 5.05 mmol) was added and the solution was stirred for 96 hours. The solution was partitioned between ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H_2O and saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided the

protected hydroxamate as a clear, colorless oil (1.26 g, 53 %).

Part D: To a solution of the protected hydroxamate of part C (1.26 g, 1.96 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in 1,4-dioxane (10 mL) and the solution was stirred for 2 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (455 mg, 47 %). HPLC purity: 98 %. MS(CI) MH^+ calculated for $C_{19}H_{19}N_2O_6SF_3$: 461, found 461. HRMS calculated for $C_{19}H_{19}N_2O_6SF_3$: 461.0994, found 461.0997. Analytical calculation for $C_{19}H_{19}N_2O_6SF_3 \bullet 1.0HCl$: C, 45.93; H, 4.06; N, 5.64; S, 6.45; Cl, 6.45. Found: C, 46.23; H, 4.07; N, 5.66; S, 6.59; Cl, 7.03.

Example 411: Preparation of 1-cyclopropyl-4-[[4-[(2,3-dihydro-1,4-benzodioxin-6-yl)amino]-phenyl]sulfonyl]-N-hydroxy-4-piperidine-carboxamide, monohydrochloride



Part A: To a solution of ester of part C, Example 91 (1.57 g, 3.40 mmol) in 1,4-dioxane (5 mL) was added 4M HCl in 1,4-dioxane (10 mL). After

stirring for one hour the resulting precipitate was collected by vacuum filtration to provide the amine hydrochloride salt as a white solid (1.16 g, 86 %).

Part B: To a slurry of the amine hydrochloride salt of part A (1.16 g, 2.91 mmol) in methanol (10 mL) was added acetic acid (1.68 mL, 29.1 mmol) followed by (1-ethyoxycyclopropyl)-oxytrimethylsilane (3.51 mL, 17.5 mmol) and sodium cyanoborohydride (823 mg, 13.1 mmol). The solution was heated to reflux for six hours. The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved into ethyl acetate and washed with H_2O, aqueous sodium hydroxide and saturated NaCl and dried over $MgSO_4$. Concentration *in vacuo* provided the N-cyclopropyl compound as a white solid (1.03 g, 88 %).

Part C: To a solution of the N-cyclopropyl compound of part B (1.0 g, 2.49 mmol) in toluene (6 mL) was added cesium carbonate (1.14 g, 3.49 mmol), tris(dibenzylideneacetone)dipalladium(0) (69 mg, 0.075 mmol) R-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (69 mg, 0.112 mmol) and 1,4-benzodioxane-6-amine (451 mg, 2.99 mmol) and the solution was heated to one hundred degrees Celsius for 19 hours. The solution was diluted with ethyl ether and filtered through Super Cel®. The filtrate was concentrated and chromatography (on silica, ethyl acetate/hexane) provided the aniline compound as an orange oil (561 mg, 48 %). MS(CI) MH^+ calculated for $C_{24}H_{28}N_2O_6S$: 473, found 473.

Part D: To a solution of the aniline compound of part C (550 mg, 1.16 mmol) in tetrahydrofuran (10 mL) was added potassium

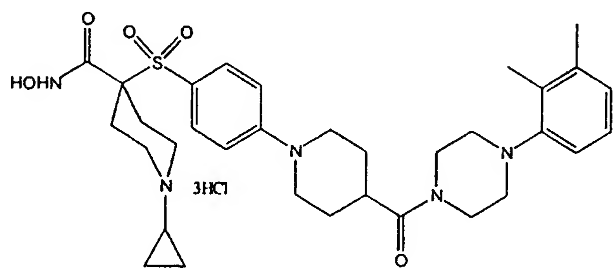
trimethylsilanolate (297 mg, 3.48 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated and the resulting residue was suspended in H_2O. The solid was collected by vacuum filtration to provide the crude acid (282 mg).

Part E: To a solution of the crude acid of part D (282 mg, 0.62 mmol) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (100 mg, 0.74 mmol), 4-methylmorpholine (0.20 mL, 1.86 mmol), and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (108 mg, 0.93 mmol). After stirring for 30 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (166 mg, 0.87 mmol) was added and the solution was stirred for 72 hours. The solution was partitioned between ethyl acetate and H_2O and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O and saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (150 mg, 43 %). MS(CI) MH^+ calculated for $C_{28}H_{35}N_3O_7S$: 558, found 558.

Part F: To a solution of protected hydroxamate of part E (133 mg, 0.24 mmol) in 1,4-dioxane (5 mL) was added 4N HCl in 1,4-dioxane (10 mL) and the solution was stirred for 1.5 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title hydroxamate as a white solid (80 mg, 66 %). MS(CI) MH^+ calculated for $C_{23}H_{27}N_3O_6S$: 474, found 474. HRMS calculated for $C_{23}H_{27}N_3O_6S$: 474.1699, found 474.1715. Analytical

calculation for $C_{23}H_{27}N_3O_6S \bullet 1.5HCl \bullet 1.5H_2O$: C, 49.75; H, 5.72; N, 7.57; S, 5.77; Cl, 9.58. Found: C, 49.78; H, 5.52; N, 8.05; S, 9.16; Cl, 5.76.

Example 412: Preparation of 1-cyclopropyl-4-[[4-[4-[[4-(2,3-dimethylphenyl)-1-piperazinyl]-carbonyl]-1-piperidinyl]phenyl]sulfonyl]-N-hydroxy-4-piperidine-carboxamide, trihydrochloride



Part A: To a solution of the isonipecotic acid (10.5 g, 81.3 mmol) in H_2O (325 mL) was added sodium carbonate (8.37 g, 81.3 mmol) and the solution was stirred until homogeneous. To this solution was added di-tert-butyl dicarbonate (18.22 g, 83.5 mmol) in 1,4-dioxane (77 mL) dropwise, and the resulting solution was stirred for 72 hours at ambient temperature. The solution was concentrated *in vacuo* and the resulting aqueous solution was washed with ethyl ether. The aqueous solution was acidified to pH=2 with concentrated HCl. The solution was extracted with ethyl ether and concentrated *in vacuo* provided a white solid. Recrystallization (ethyl

acetate) provided N-Boc-isonipecotic acid as a white solid (10 g, 54 %).

Part B: To a solution of the N-Boc-isonipecotic acid of part A (2.14 g, 9.33 mmol) in dichloromethane (19 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.82 g, 9.49 mmol), N-hydroxybenzotriazole (1.32 g, 9.77 mmol) and 1-(2,3-xylyl)piperazine monohydrochloride (2.47 g, 10.89 mmol). After 30 minutes diisopropylethylamine (0.74 mL, 20.7 mmol) was added, and the solution was stirred for 18 hours. The solution was concentrated *in vacuo* and the residue was dissolved into ethyl acetate and washed with 1M HCl, saturated $NaHCO_3$ and saturated NaCl. The solution was dried over $MgSO_4$. Recrystallization (ethyl acetate/hexane) provided the amide as an off-white solid (2.65 g, 71 %).

Part C: To a solution of the amide of part B (1.0 g, 3.75 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL) and the solution was stirred for 15 minutes. The solution was concentrated *in vacuo* and the resulting oil was dissolved into N,N-dimethylacetamide (10 mL). To this solution was added the product of Example 398, Part A (979 mg, 2.50 mmol) and cesium carbonate (3.67 g, 11.25 mmol) and the solution was heated at one hundred and ten degrees Celsius for 17 hours. The solution was partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the piperidine compound as a white solid (1.89 g, quantitative yield). MS(CI) MH^+ calculated for $C_{35}H_{48}N_4O_5S$: 637, found 637.

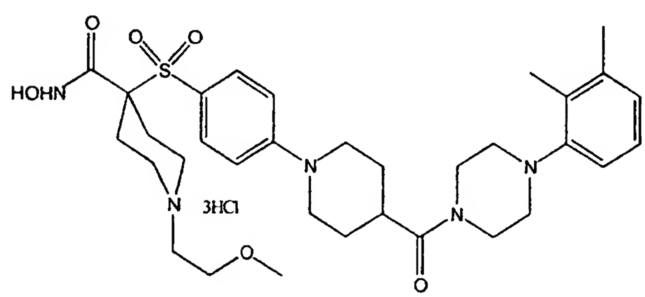
Part D: To a solution of the piperidine compound of part C (1.89 g) in ethanol (8 mL) and tetrahydrofuran (8 mL) was added sodium hydroxide (1.0 g, 25 mmol) in H_2O (5 mL). The solution was heated to fifty degrees Celsius for 8 hours and at sixty-two degrees Celsius for 8 hours. The solution was concentrated *in vacuo* and the residue was diluted with H_2O and acidified to pH = 3 with 3M HCl. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (1.16 g, 65 %). MS(CI) MH^+ calculated for $C_{33}H_{44}N_4O_5S$: 609, found 609.

Part E: To a solution of the acid of part D (1.16 g, 1.62 mmol) in N,N-dimethylformamide (10 mL) were added N-hydroxybenzotriazole (262 mg, 1.94 mmol), 4-methylmorpholine (0.90 mL, 8.2 mmol) and O-(tetrahydro-2H-pyran-2-y)l hydroxylamine (284 mg, 2.4 mmol). After stirring for 45 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (334 mg, 2.2 mmol) was added and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O and the organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Trituration (dichloromethane) provided the protected hydroxamate as a white solid (850 mg, 75 %). MS(CI) MH^+ calculated for $C_{38}H_{53}N_5O_6S$: 708, found 708. Analytical calculation for $C_{38}H_{53}N_5O_6S \bullet 0.5H_2O$: C, 63.66; H, 7.59; N, 9.77; S, 4.47. Found: C, 63.68; H, 7.54; N, 9.66; S, 4.67.

Part F: To a solution of the protected hydroxamate of part E (746 mg, 1.07 mmol) in methanol (10 mL) was added 4M HCl in 1,4-dioxane (10 mL) and

the solution was stirred for one hour. The resulting solid was collected by vacuum filtration and washed with ethyl ether to provide the title compound as a white solid (650 mg, 83 %). MS(CI) MH^+ calculated for $C_{33}H_{45}N_5O_5S$: 624, found 624. HRMS calculated for $C_{33}H_{49}N_5O_5S$: 624.3220, found 624.3253. Analytical calculation for $C_{33}H_{45}N_5O_5S \bullet 3.5HCl \bullet H_2O$: C, 51.82; H, 6.59; N, 9.16. Found: C, 52.04; H, 6.30; N, 8.96.

Example 413: Preparation of 4-[[4-[4-[[4-(2,3-dimethylphenyl)-1-piperazinyl] carbonyl]-1-piperidinyl]phenyl] sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidine-carboxamide, trihydrochloride



Part A: To a solution of the isonipecotic acid (10.5 g, 81.3 mmol) in H_2O (325 mL) was added sodium carbonate (8.37 g, 81.3 mmol) and the solution was stirred until homogeneous. To this solution was added di-tert-butyl dicarbonate (18.22 g, 83.5 mmol) in 1,4-dioxane (77 mL) dropwise and the resulting solution was stirred for 72 hours at ambient temperature. The solution was concentrated *in vacuo* and the resulting aqueous solution was washed with

ethyl ether. The aqueous solution was acidified to pH=2 with concentrated HCl. The solution was extracted with ethyl ether and concentration *in vacuo* provided a white solid. Recrystallization (ethyl acetate) provided N-Boc-isonipecotic acid as a white solid (10 g, 54 %).

Part B: To a solution of the N-Boc-isonipecotic acid of part A (2.14 g, 9.33 mmol) in dichloromethane (19 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.82 g, 9.49 mmol), N-hydroxybenzotriazole (1.32 g, 9.77 mmol) and 1-(2,3-xylyl)piperazine monohydrochloride (2.47 g, 10.89 mmol). After 30 minutes, diisopropylethylamine (0.74 mL, 20.7 mmol) was added and the solution was stirred for 18 hours. The solution was concentrated *in vacuo* and the residue was dissolved into ethyl acetate and washed with 1M HCl, saturated $NaHCO_3$ and saturated NaCl. The solution was dried over $MgSO_4$. Recrystallization (ethyl acetate/hexane) provided the amide as an off-white solid (2.65 g, 71 %).

Part C: To a solution of the amide of part B (965 mg, 2.41 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL) and the solution was stirred for 15 minutes. The solution was concentrated *in vacuo* and the resulting oil was dissolved into N,N-dimethylacetamide (10 mL). To this solution were added ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (600 mg, 1.61 mmol) and cesium carbonate (2.75 g, 8.43 mmol), and the solution was heated at one hundred and ten degrees Celsius for 20 hours. The solution was partitioned between ethyl

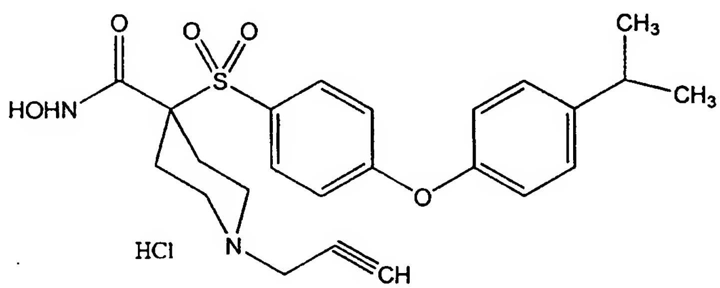
acetate and H_2O. The organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the piperidine compound as a white solid (1.26 g, quantitative yield). MS(CI) MH^+ calculated for $C_{35}H_{50}N_4O_6S$: 655, found 655.

Part D: To a solution of the piperidine compound of part C (1.26 g) in ethanol (5 mL) and tetrahydrofuran (5 mL) was added sodium hydroxide (644 mg, 16 mmol) in H_2O (5 mL). The solution was heated to sixty degrees Celsius for 8 hours and at sixty-two degrees Celsius for 8 hours. The solution was concentrated *in vacuo* and the residue was diluted with H_2O and acidified to pH = 3 with 3M HCl. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (650 mg, 65 %). MS(CI) MH^+ calculated for $C_{33}H_{46}N_4O_6S$: 627, found 627.

Part E: To a solution of the acid of part D (620 g, 0.94 mmol) in N,N-dimethylformamide (10 mL) were added N-hydroxybenzotriazole (152 mg, 1.13 mmol), 4-methylmorpholine (0.52 mL, 4.7 mmol) and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (165 mg, 1.4 mmol). After stirring for 45 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (252 mg, 1.32 mmol) was added and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O, and the organic layer was washed with H_2O and saturated NaCl, and dried over Na_2SO_4. Concentration *in vacuo* provided the protected hydroxamate as a white solid (641 mg, 94 %). MS(CI) MH^+ calculated for $C_{38}H_{55}N_5O_7S$: 726, found 726.

Part F: To a solution of the protected hydroxamate of part E (630 mg, 0.87 mmol) in methanol (8 mL) was added 4M HCl in 1,4-dioxane (10 mL) and the solution was stirred for one hour. The resulting solid was collected by vacuum filtration and washed with ethyl ether to provide the title compound as a white solid (624 mg, 83 %). MS(CI) MH^+ calculated for $C_{33}H_{47}N_5O_6S$: 642, found 642.

Example 414: Preparation of N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohdyrochloride



Part A: To a solution of the product of Example 9, Part E (6.0 g, 15.4 mmol) and powdered K_2CO_3 (8.0 g, 38.5 mmol) in N,N-dimethylformamide (70 mL) was added 4-isopropyl phenol (5.24 g, 38.5 mmol) at ambient temperature, and the solution was heated to ninety degrees Celsius for 32 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the diaryl ether as light yellow gel (6.89 g, 87%).

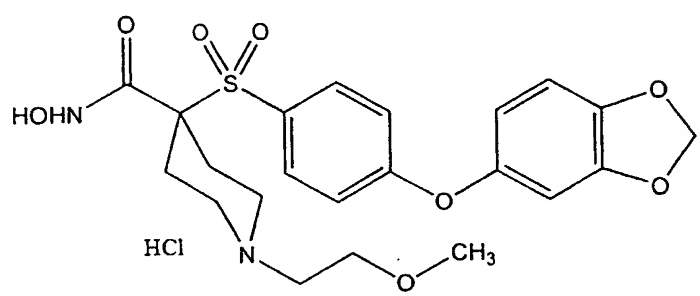
Part B: To a solution of diaryl ether of part A (6.89 g, 14.7 mmol) in ethanol (14 mL) and tetrahydrofuran (14 mL) was added NaOH (5.88 g, 147 mmol) in H_2O (28 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 17 hours and ambient temperature for 24 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH = 2. Vacuum filtration of white precipitation provided the acid as a white solid (6.56 g, quantitative yield).

Part C: To the solution of acid of part B (6.56 g, 14.86 mmol), N-methyl morpholine (6.5 mL, 59.4 mmol), 1-hydroxybenzotriazole (6.0 g, 44.6 mmol) and O-tetrahydropyranyl hydroxyl amine (3.5 g, 29.7 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.5 g, 44.6 mmol), and the solution was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (8.03 g, quantitative yield).

Part D: To a solution of 4N HCl in dioxane (37 mL, 149 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (8.03 g, 14.9 mmol) in methanol (5 mL) and dioxane (15 mL) and the solution was stirred at ambient

temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (5.0 g, 71.1%). Analytical calculation for $C_{24}H_{28}N_2O_5S.HCl.0.9H_2O$: C, 56.61; H, 6.10; N, 5.50; S, 6.30. Found: C, 56.97; H, 6.05; N, 5.41; S, 5.98. HRMS MH^+ calculated for $C_{24}H_{28}N_2O_5S$: 457.1797, found 457.1816.

Example 415: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl)sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (25 g, 67.3 mmol) and powdered K_2CO_3 (23.3 g, 169 mmol) in N,N-dimethylformamide (150 mL) was added sesamol (23.2 g, 168 mmol) at ambient temperature and solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the

desired diaryl ether as light yellow gel (33.6 g, 93.6%).

Part B: To a solution of diaryl ether of part A (4.0 g, 7.4 mmol) in dichloromethane (7 mL) cooled to zero degrees Celsius was added trifluroacetic acid (7 mL) and the solution was stirred at ambient temperature for 2 hours. Concentration *in vacuo* provided the amine trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate salt and K_2CO_3 (3.6 g, 26 mmol) in N,N-dimethylformamide (50 mL) was added 2-bromoethyl methyl ether (1.8 mL, 18.7 mmol) and the solution was stirred at ambient temperature for 36 hours. The N,N-dimethylformamide was evaporated under high vacuum and residue was diluted with ethyl acetate. The organic layer was washed with water and dried over Mg_2SO_4. Concentration *in vacuo* provided the methoxyethyl amine as a light yellow gel (3.7 g, quantitative yield).

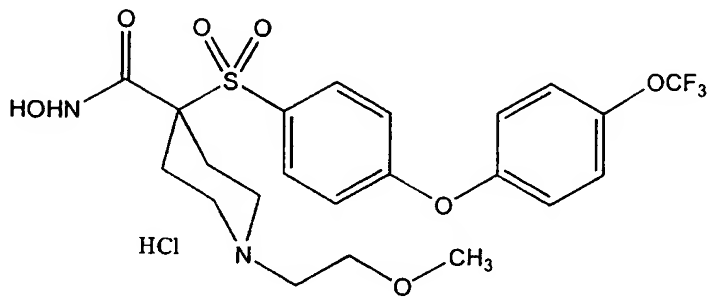
Part C: To a solution of methoxyethyl amine of part B (3.7 g, 7.5 mmol) in ethanol (7 mL) and tetrahydrofuran (7 mL) was added NaOH (3.0 g, 75 mmol) in H_2O (15 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 19 hours and ambient temperature for 12 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (4.0 g, quantitative yield).

Part D: To a solution of the acid of part C (4.0 g, 7.5 mmol), N-methyl morpholine (3.3 mL, 30

mmol), 1-hydroxybenzotriazole (3.0 g, 22.5 mmol) and O-tetrahydropyranyl hydroxyl amine (1.8 g, 15 mmol) in N,N-dimethylformamide (100 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.3 g, 22.5 mmol), and the solution was stirred at ambient temperature for 4 days. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over Mg_2SO_4. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (2.40 g, 57.1%).

Part E: To a solution of 4N HCl in dioxane (11 mL, 43 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part D (2.4 g, 4.3 mmol) in methanol (2 mL) and dioxane (6 mL) and the solution was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with ether provided hydroxamate hydrochloride salt as a white solid (1.88 g, 85.8%). Analytical calculation for $C_{22}H_{26}N_2O_8S.HCl.H_2O$: C, 49.58; H, 5.48; N, 5.26; S, 6.02. Found: C, 49.59; H, 5.53; N, 5.06; S, 5.71. HRMS MH^+ calculated for $C_{22}H_{26}N_2O_8S$: 479.1488, found 479.1497.

Example 416: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl}-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (30 g, 161 mmol) in dichloromethane (50 mL) cooled to zero degrees Celsius was added trifluroacetic acid (25 mL) and the solution was stirred at ambient temperature for 1 hour. Concentration *in vacuo* provided the amine trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate salt and K_2CO_3 (3.6 g, 26 mmol) in N,N-dimethylformamide (50 mL) cooled to zero degrees Celsius was added 2-bromoethyl methyl ether (19 mL, 201 mmol), and solution was stirred at ambient temperature for 36 hours. Then, N,N-dimethylformamide was evaporated under high vacuum and the residue was diluted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. Concentration *in vacuo* provided the methoxyethyl amine as a light yellow gel (26.03 g, 86.8%).

Part B: To a solution of methoxyethyl amine (6.0 g, 16.0 mmol) of part A and powdered K_2CO_3 (4.44 g, 32 mmol) in N,N-dimethylformamide (30 mL) was added 4-(trifluoromethoxy)phenol (5.72 g, 32 mmol) at ambient temperature and the solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was

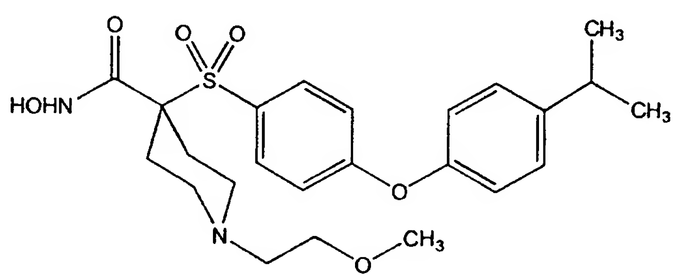
dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided trifluoromethoxy phenoxyphenyl sulfone as a light yellow gel (7.81 g, 91.5%).

Part C: To a solution of trifluoromethoxy phenoxyphenyl sulfone of part B (7.81 g, 14.7 mmol) in ethanol (14 mL) and tetrahydrofuran (14 mL) was added NaOH (5.88 g, 147 mmol) in H_2O (28 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of white precipitation provided the acid as a white solid (5.64 g, 73.3%).

Part D: To a solution of the acid of part C (5.64 g, 10.8 mmol), N-methyl morpholine (4.8 mL, 43.1 mmol), 1-hydroxybenzotriazole (4.38 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.5 g, 21.6 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.2 g, 32.4 mmol), and the solution was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (6.65 g, quantitative yield).

Part E: To a solution of 4N HCl in dioxane (28 mL, 110 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part D (6.65 g, 11.03 mmol) in methanol (3 mL) and dioxane (9 mL) and was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (4.79 g, 78.2%). Analytical calculation for $C_{22}H_{25}N_2O_7SF_3.HCl.0.5H_2O$: C, 46.85; H, 4.83; N, 4.97; S, 5.69. Found: C, 46.73; H, 4.57; N, 4.82; S, 5.77.

Example 417: Preparation of <u>N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(1-methylethyl)-phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride</u>



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.47 g, 3.9 mmol) and powdered K_2CO_3 (1.6 g, 11.7 mmol) in N,N-dimethylformamide (15 mL) was added 4-isopropylphenol (1.07 g, 7.8 mmol) at ambient temperature and the solution was heated to ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$.

Chromatography on silica eluting with ethyl acetate/hexane provided the diaryl ether as a light yellow gel (1.77 g, 92.2%).

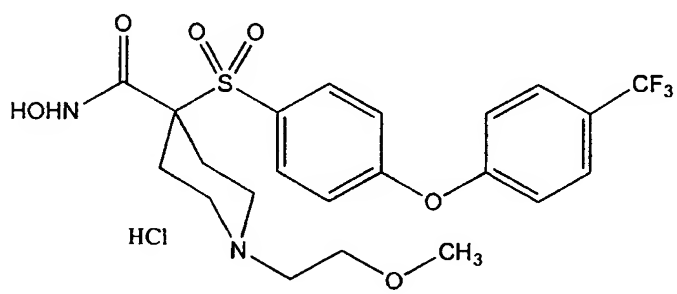
Part B: To a solution of diaryl ether of part A (1.77 g, 3.6 mmol) in ethanol (3.5 mL) and tetrahydrofuran (3.5 mL) was added NaOH (1.46 g, 36 mmol) in H_2O (7 mL) at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (1.39 g, 83.7%).

Part C: To the solution of the acid of part B (1.39 g, 3.0 mmol), N-methyl morpholine (1 mL, 9 mmol), 1-hydroxybenzotriazole (1.22 g, 9 mmol) and O-tetrahydropyranyl hydroxyl amine (0.72 g, 6.0 mmol) in N,N-dimethylformamide (90 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.72 g, 9.0 mmol), and solution was stirred at ambient temperature for 48 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (1.65 g, 98.2%).

Part D: To a solution of 4N HCl in dioxane (7.35 mL, 29.4 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (1.65 g, 2.94 mmol) in methanol (1 mL) and dioxane (3

mL), and the solution was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (1.2 g, 79.5%). Analytical calculation for $C_{24}H_{32}N_2O_6S.HCl.0.5H_2O$: C, 55.22; H, 6.56; N, 5.37; S, 6.14. Found: C, 55.21; H, 6.41; N, 5.32; S, 6.18.

Example 418: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoro methyl)-phenoxy]phenyl]sulfonyl}-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (6 g, 16.0 mmol) and powdered K_2CO_3 (4.44 g, 32 mmol) in N,N-dimethylformamide (50 mL) was added 4-trifluoromethylphenol (5.72 g, 32 mmol) at ambient temperature, and the solution was heated to ninety degrees Celsius for 48 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (2.66 g, 32.1%).

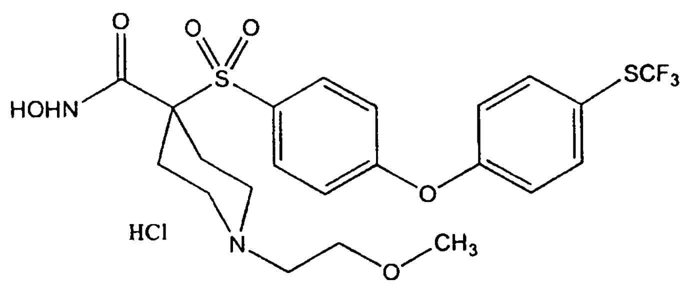
Part B: To a solution of the diaryl ether of part A (1.5 g, 2.9 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was added NaOH (1.22 g, 29 mmol) in H_2O (6 mL) at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the desired acid as a white solid (1.0 g, 70.9%).

Part C: To the solution of the acid of part B (1.0 g, 2.05 mmol), N-methyl morpholine (0.68 mL, 6.1 mmol), 1-hydroxybenzotriazole (0.84 g, 6.15 mmol) and O-tetrahydropyranyl hydroxyl amine (0.5 g, 4.1 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.18 g, 6 mmol), and solution was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (1.16 g, 96.7%).

Part D: To a solution of 4N HCl in dioxane (5 mL, 20 mmol)) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (1.16 g, 2 mmol) in methanol (1 mL) and dioxane (3 mL) and was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (0.79 g, 74.5%). Analytical calculation for

$C_{22}H_{25}N_2O_6SF_3$.HCl: C, 49.03; H, 4.86; N, 5.20; S, 5.95. Found: C, 48.85; H, 4.60; N, 5.22; S, 6.13.

Example 419: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-[(trifluoromethyl)thio]phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (5 g, 13.4 mmol) and powdered K_2CO_3 (3.7 g, 27 mmol) in N,N-dimethylformamide (20 mL) was added 4-(trifluoromethylthio)phenol (3.9 g, 20 mmol) at ambient temperature, and solution was heated to ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum, and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (5.94 g, 81.04%).

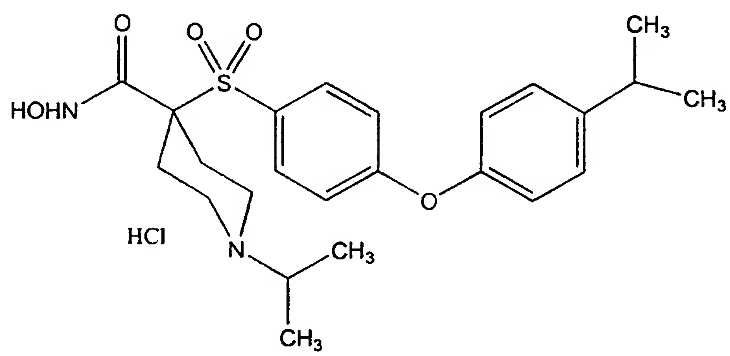
Part B: To a solution of the diaryl ether of part A (5.94 g, 210 mmol) in ethanol (10 mL) and tetrahydrofuran (10 mL) was added NaOH (4.34 g, 108 mmol) in H_2O (20 mL) dropwise at ambient temperature.

The solution was then heated to sixty degrees Celsius for 24 hours and ambient temperature for anther 24 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (5.5 g, quantitative yield).

Part C: To the solution of the acid of part B (5.5 g, 10.8 mmol), N-methyl morpholine (3.6 mL, 32.4 mmol), 1-hydroxybenzotriazole (4.4 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.6 g, 21.8 mmol) in N,N-dimethylformamide (200 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.2 g, 32.4 mmol), and the solution was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (4.66 g, 69.8%).

Part D: To a solution of 4N HCl in dioxane (20 mL, 79 mmol)) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (4.65 g, 7.9 mmol) in methanol (2.5 mL) and dioxane (8 mL) and was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (3.95 g, 92.1%). Analytical calculation for $C_{22}H_{25}N_2O_6S_2F_3.HCl$: C, 46.27; H, 4.59; N, 4.91; S, 11.23. Found: C, 46.02; H, 4.68; N, 4.57; S, 11.11.

Example 420: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-[4-(1-methylethyl)-phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (30 g, 161 mmol) in dichloromethane (40 mL) cooled to zero degrees Celsius was added trifluroacetic acid (30 mL), and the solution was stirred at ambient temperature for 1 hour. Concentration *in vacuo* provided the trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate salt and triethylamine (28 mL, 201 mmol) in dichloromethane (250 mL) cooled to zero degrees Celsius, were added acetone (24 mL, 320 mmol) and sodium triacetoxyborohydride (68 g, 201 mmol) in small portions followed by addition of acetic acid (18.5 mL, 320 mmol), and solution was stirred at ambient temperature for 48 hours. Then, the dichloromethane was evaporated under high vacuum and the residue was diluted with diethyl ether. The organic layer was washed with 1N NaOH, water and

dried over $MgSO_4$. Concentration *in vacuo* provided the isopropyl amine as a light yellow gel (21.03 g, 72.8%).

Part B: To a solution of isopropyl amine (4 g, 11.2 mmol) of part A and powdered K_2CO_3 (3.09 g, 22.4 mmol) in N,N-dimethylformamide (30 mL) was added 4-isopropylphenol (3.05 g, 22 mmol) at ambient temperature and the solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (5.10 g, 96.2%).

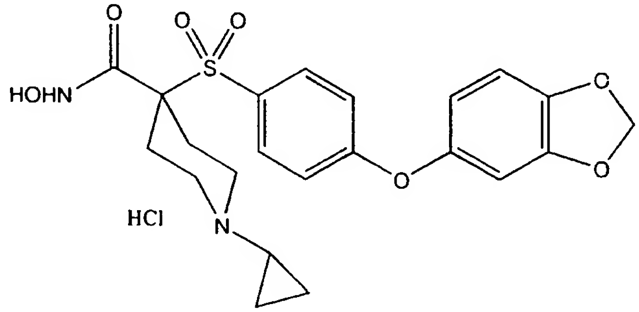
Part C: To a solution of the diaryl ether of part B (5.10 g, 10.77 mmol) in ethanol (10 mL) and tetrahydrofuran (10 mL) was added NaOH (4.3 g, 108 mmol) in H_2O (20 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 24 hours and at ambient temperature for anther 24 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the desired acid as a white solid (4.80 g, quantitative yield).

Part D: To the solution of the acid of part C (4.80 g, 10.8 mmol), N-methyl morpholine (3.6 mL, 32.4 mmol), 1-hydroxybenzotriazole (4.4 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.6 g, 21.6 mmol) in N,N-dimethylformamide (100 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

hydrochloride (6.17 g, 32.4 mmol), and the solution was stirred at ambient temperature for 7 days. The solution was filtered to eliminate the unreacted starting material and the filtrate was concentrated under high vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and dried over $MgSO_4$. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (2.45 g, 41.7%).

Part E: To a solution of 4N HCl in dioxane (11.2 mL, 45 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part D (2.45 g, 11.03 mmol) in methanol (4 mL) and dioxane (8 mL) and was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and tituration with diethyl ether provided the title compound as a white solid (2.01 g, 89.7%). Analytical calculation for $C_{24}H_{32}N_2O_5S.HCl.0.5H_2O$: C, 56.96; H, 6.77; N, 5.54; S, 6.34. Found: C, 56.58; H, 6.71; N, 5.44; S, 6.25.

Example 421: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-1-cyclopropyl-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A : To a solution of the product of Example 9, Part D (9.0 g, 22.0 mmol) in DMF (30 mL) was added K_2CO_3 (4.55 g, 33 mmol), and sesamol (4.55 g, 33 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo.* Chromatography on silica gel eluting with 10% ethyl acetate/hexane provided the desired ester as an oil (9.3 g, 79%). HRMS MH^+ calculated for $C_{26}H_{31}NSO_9$: 534.1798, found 534.1796..

Part B: To a solution of the ester of part A (9.3 g, 17 mmol) in ethyl acetate (100 mL) cooled to zero degrees C was bubbled gaseous HCl for 10 minutes. The reaction was stirred at this temperature for 0.5 hours. The solution was concentrated *in vacuo* to give the hydrochloride salt (7.34 g, 92%). MS MH^+ calculated for $C_{21}H_{23}NSO_7$: 434.1273, found 434.1285..

Part C: To a solution of the hydrochloride salt of part B (7.34 g, 15.6 mmol) in methanol (60 mL) was added acetic acid (8.94 mL, 156 mmol), a portion (about 2 g) of 4-Å molecular sieves, (1-ethoxycyclopropyl)-oxytrimethyl silane (18.82 mL, 93.6 mmol) and sodium cyanoborohydride (4.41 g, 70.2

mmol). The solution was refluxed for 8 hours. The precipitate was removed by filtration and the filtrate concentrated *in vacuo*. The residue was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 100% ethyl acetate) provided the desired cyclopropyl amine as a solid (7.9 gm, 100%). MS MH^+ calculated for $C_{24}H_{27}NSO_7$: 474.1586, found 474.1599.

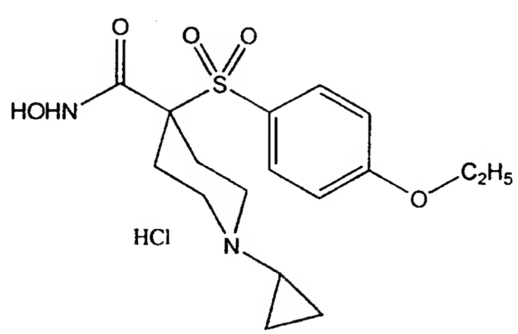
Part D: To a solution of cyclopropyl amine from part C (7.9 g, 16.7 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.68 g, 166.8mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3. The resulting precipitate was filtered to give desired carboxylic acid (6.14 g, 76%). MS MH^+ calculated for $C_{22}H_{25}NSO_7$: 446.1273. Found 446.1331.

Part E: To a solution of the carboxylic acid of part D (6.14 g, 12.7mmol) in DMF (60 mL) was added 1-hydroxybenzotriazole (2.06 g, 15.2 mmol), N-methyl morpholine (4.2 mL, 38.0 mmol) and O-tetrahydropyranyl hydroxyl amine (2.23 g, 19.0 mmol) followed by 1,3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.41 g, 17.8 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 40% ethyl acetate/hexane

provided the desired tetrahydropyranyl-protected hydroxamate as a solid (6.67 g, 96%).

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (6.67 g, 12.0 mmol) in dioxane (70 mL) was added 4 N HCl/dioxane (6.6 mL). After stirring at ambient temperature for 3 hours, the solution was concentrated *in vacuo*. Chromatography on a C18 reverse phase column, eluting with acetonitrile/(HCl)water, provided a white solid (4.21 gm, 69%). MS MH^+ calculated for $C_{22}H_{24}N_2SO_7$: 461.1382. Found 461.1386.

Example 422: Preparation of 1-cyclopropyl-4-[[4-(4-ethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (8.0 g, 19.2 mmol) in DMF (30 mL) was added K_2CO_3 (4.00 g, 28.8 mmol) and 4-ethoxyphenol (3.99 g, 28.8 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated

in vacuo. Chromatography on silica gel eluting with 10% ethyl acetate/hexane provided the desired ester as an oil (9.62 g, 94 %). MS MH^+ calculated for $C_{27}H_{35}NSO_8$: 534.2162. Found 534.2175.

Part B: To a solution of ester of part A (9.62 g, 18 mmo) in ethyl acetate (100 mL) cooled to zero degrees Celcius was bubbled gaseous HCl for 5 minutes. The reaction was stirred at this temperature for 0.5 hours. The solution was then concentrated *in vacuo* to give a the hydrochloride salt (8.1 g, 96%). MS MH^+ calculated for $C_{22}H_{27}NSO_6$: 434.1637. Found 434.1637.

Part C: To a solution of the hydrochloride salt of part B (8.1 g, 17.2 mmol) in methanol (70 mL) was added acetic acid (9.86 mL, 172 mmol), a portion of 4-Å molecular sieves (ca. 2 g), (1-ethoxycyclopropyl)-oxytrimethyl silane (20.7 mL, 103 mmol) and sodium cyanoborohydride (4.86 g, 77.4 mmol). The solution was refluxed for 8 hours. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with 1 N NaOH, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Trituration with diethyl ether provided the desired cyclopropyl amine as a white solid (6.84 g, 84%).

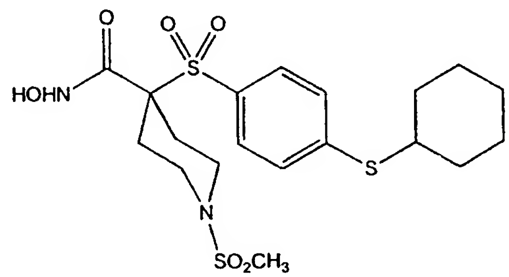
Part D: To a solution of cyclopropyl amine from part C (6.84gm, 14.0 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (5.60 g, 140 mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the

aqueous residue was acidified to pH=3. Filtration gave the desired acid (6.07 g, 88%). MS MH$^+$ calculated for $C_{22}H_{27}NSO_6$: 446. Found 446.

Part E: To a solution of the acid of part D (6.07g, 12.6 mmol) in DMF (60 mL) was added 1-hydroxybenzotriazole (2.04 g, 15.1 mmol), N-methyl morpholine (4.15 mL, 37.8 mmol) and O-tetrahydropyranyl hydroxyl amine (2.21 g, 18.9 mmol) followed by 1,3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.38 g, 17.6 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 60% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white foam (6.29 g, 92%). MS MH$^+$ calculated for $C_{28}H_{36}N_2SO_7$: 545.2321. Found 545.2316.

Part F: To a solution of the tetrahydropyranyl-protected hydroxamate of part E (2.84 g, 5.0 mmol) in dioxane (40 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated *in vacuo*. Trituration of the resulting solid with diethyl ether and filtration gave the desired hydroxamate as a white solid (2.33 g, 90%). MS M$^+$ calculated for $C_{23}H_{28}N_2SO_6$: 460.1677. Found 460.1678.

Example 423: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-1-(methylsulfonyl)-4-piperidinecarboxamide



Part A: To a solution of the product of Example 9, Part D (10.0 g, 24.0 mmol) in DMF (20 mL) was added K_2CO_3 (4.99 g, 36.0mmol), cyclohexyl mercaptan (4.40 g, 36.0 mmol). The solution was stirred at ninety degrees Celsius for 48 hrs. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Trituration with ethanol provided the desired sulfide as a white solid (7.16 g, 58%).

Part B: To a solution of sulfide from part B (9.46 g, 18.5 mmol) in ethanol (30 mL) and tetrahydrofuran (30 mL) was added a solution of NaOH (7.39 g, 185 mmol) in water (15 mL) and the solution was heated at sixty-five degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH = 3.5. The resulting white solid was collected by filtration washed with H_2O and ethyl ether to give desired carboxylic acid (8.57 g, 95%).

Part C: To a solution of carboxylic acid of part B (8.3 g, 17.0 mmol) in ethyl acetate (200 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 15 min. The reaction was then stirred at this temperature for 0.5 hour. The solution was concentrated *in vacuo* to afford a residue which was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (7.03 g, 98%). MS MH+ calculated for $C_{18}H_{25}NS_2O_4$: 384.1303. Found 384.1318.

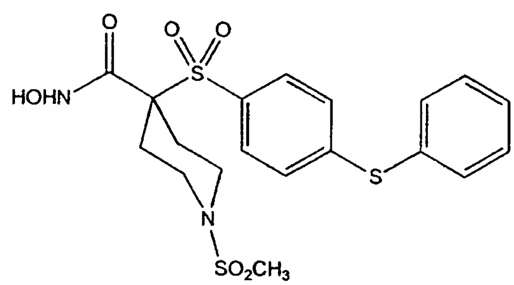
Part D: To a solution of the hydrochloride salt of part C (1.0 g, 2.4 mmol) was added N-methyl morpholine (654 mL, 5.9 mmol) followed by mesyl chloride (280 mL, 3.6 mmol) in methylene chloride (20 mL). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with methylene chloride. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired methanesulfomanide as a foam (1.0 g, quantitative yield)

Part E: To a solution of the methanesulfonamide of part D (1.3 g, 2.9 mmol) in DMF (30 mL) was added 1-hydroxybenzotriazole (474 mg, 3.5 mmol), N-methyl morpholine (956 mL, 8.7 mmol), tetrahydropyranyl hydroxyl amine (509 mg, 4.3 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (778 mg, 4.06 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica

gel eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white foam (1.05 g, 82%).

Part F: To a solution of the tetrahydropyranyl-protected hydroxamate of part E (1.05 g, 1.97 mmol) in dioxane (30 mL) was added 4 N HCl/dioxane (10 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated *in vacuo*. Chromatography on C18 reverse phase column eluting with acetonitrile/(HCl) water provided a white solid (602 mg, 64%). MS M^+ for $C_{19}H_{28}N_2S_3O_6$: 477, found 477.

Example 424: Preparation of N-hydroxy-1-(methylsulfonyl)-4-[[4-(phenylthio)-phenyl]sulfonyl]-4-piperidinecarboxamide



Part A: To a solution of the product of Example 9, Part D (40.0 g, 96.0 mmol) in DMF (200 mL) was added K_2CO_3 (20 g, 144 mmol) and thiophenol (22.2 g, 144 mmol). The solution was stirred at ambient temperature for 24 hrs. The solution was then diluted with H_2O (1 L) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (on silica,

elueting with 15% ethyl acetate/hexane) provided the desired sulfide as a white solid (44.4 g, 91%).

Part B: To a solution of sulfide of part A (31.2 g, 6.6 mmol) in ethyl acetate (500 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 30 minutes. The reaction was stirred at this temperature for 1.5 hours. The solution was concentrated *in vacuo* and resulting solid was triturated with diethyl ether to provide the hydrochloride salt as a white solid (26.95 g, 96%).

Part C: To a solution of the hydrochloride salt of part B (2.0 g, 4.7 mmol), were added N-methyl morpholine (1.29 mL, 11.7 mmol), followed by mesyl chloride (550 mL, 7.05 mmol) in methylene chloride (35 mL). The solution was stirred at ambient temperature for 48 hours. The solution was diluted with H_2O (400 mL) and extracted with methylene chloride. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired methanesulfonamide as a white solid (2.17 gm, 96%).

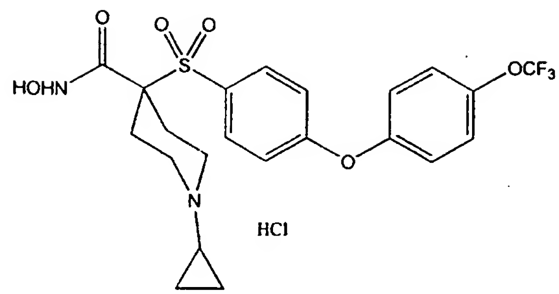
Part D: To a solution of the methane sulfonamide from part C (2.1 g, 4.3 mmol) in ethanol (25 mL) and tetrahydrofuran (25 mL) was added a solution of NaOH (1.72 g, 43 mmol) in water (10 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3.5. The resulting precipitate was filtered to give the desired carboxylic acid as a white solid (2.1 g, quantitative yield).

Part E: To a solution of the carboxylic acid of part D (1.98 g, 4.3 mmol) in DMF (30 mL) were added

1-hydroxybenzotriazole (705 mg, 5.2 mmol), N-methyl morpholine (1.54 mL, 12.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (755 mg, 6.5 mmol) followed by 1-3-(dimethylamino) propyl]-3-ethyl carbodiimide hydrochloride (1.17 g, 6.1 mmol). The solution was stirred at ambient temperature for 5 days. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on C18 reverse phase column, eluting with acetonitrile/(HCl) water provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (1.86 g, 80%). HRMS MH^+ calculated for $C_{24}H_{30}N_2S_3O_7$: 555.1293, found 555.1276.

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (1.86 g, 3.5 mmol) in dioxane (30 mL) and methanol (10 mL) was added 4 N HCl/dioxane (20 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated *in vacuo*. Chromatography on a C18 reverse phase column eluting with acetonitrile/(HCl) water provided the title compound as a white solid (1.48 gm, 91%). HRMS MH^+ calculated for $C_{19}H_{22}N_2S_3O_6$: 471.0718 Found 471.0728.

Example 425: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]-4-piperidine-carboxamide, monohydrochloride



Part A: To a solution of the product of Example 398, Part A (6.97 g, 19.6 mmol) in DMF (500 mL) was added K_2CO_3 (3.42 g, 18.0 mmol) and 4-(triflouromethoxy)-phenol (3.7 g, 24.8 mmol). The solution was stirred at ninety degrees Celsius for 40 hours. The solution was diluted with H_2O (600 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired diaryl ether as an oil (8.5 g, quantitative). HRMS MH^+ calculated for $C_{24}H_{26}NSO_6F_3$: 514.1511. Found 514.1524.

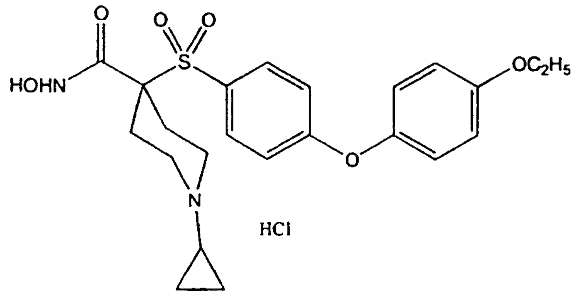
Part B: To a solution of diaryl ether from part A (8.4 g, 16.4 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.54 g, 164 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* to remove most of organic solvents and the aqueous residue was acidified to pH=4.0. The resulting precipitate was filtered to give the desired filtered to give the hydrochloride salt as a white solid (5.01 g, 63%). HRMS MH^+ calculated for $C_{22}H_{22}NSO_6F_3$: 486.1198, found 486.1200.

Part C: To a solution of the hydrochloride salt of part B (5.0 g, 10.3 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.65 g, 12.3 mmol), N-

methyl morpholine (3.4 mL, 30.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.8 g, 15.4 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.60 g, 12.3 mmol). The solution was stirred at ambient temperature for 42 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (5.41 g, 89%).

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (5.4 g, 9.2 mmol) in dioxane (80 mL) and methanol (20 mL) was added 4 N HCl/dioxane (50 mL). The reaction was stirred at ambient temperature for 2.5 hours, the solution was concentrated *in vacuo*. Trituration with diethyl ether afforded the title compound as a white solid (4.02 g, 81%). HRMS MH^+ calculated for $C_{22}H_{23}N_2SO_6F_3$: 501.1307, found 501.1324.

Example 426: Preparation of 1-cyclopropyl-4-[(4-ethoxyphenyl) sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



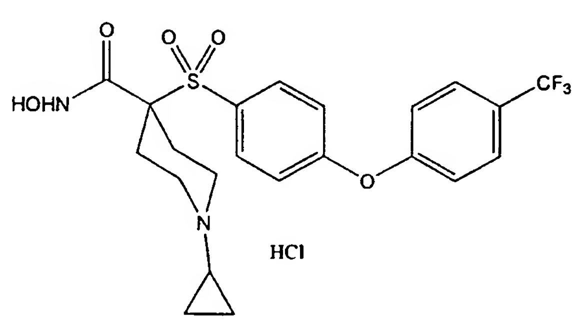
Part A: To a solution of the product of Example 398, Part A (5.87 g, 16.5 mmol) in DMF (50 mL) was added K_2CO_3 (3.42 g, 24.7 mmol) and α,α,α-(trifluoromethyl)-p-cresol (4.01g, 24.7 mmol). The solution was stirred at ninety degrees Celsius for 48 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, containing a large percentage of starting material (8.39 g). To this material (8.39 g) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.75 g, 169 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3.5. The resulting precipitate was filtered to give the desired hydrochloride salt as a waxy solid (5.04 g, 64%).

Part B: To a solution of the hydrochloride salt of part A (5.0 g, 10.3 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.73 g, 12.8 mmol), N-methyl morpholine (3.5 mL, 31.8 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.86 g, 15.9 mmol) followed by 1-3-(dimethylamino)propyl]-

3-ethylcarbodiimide hydrochloride (2.84 g, 14.8 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (1.5 g, 32%).

Part C: To a solution of tetrahydropyranyl-protected hydroxamate of part D (1.5 g, 3.3mmol) in dioxane (30 mL) and methanol (15 mL) was added 4 N HCl/dioxane (50 mL). The reaction was stirred at ambient temperature for 2 hours, then the solution was concentrated *in vacuo*. Trituration of the residue with diethyl ether afforded the title compound as a white solid (1.09g, 81%). MS MH^+ for $C_{17}H_{24}N_2SO_5$: 369 found 369.

Example 427: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl) phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 398, Part A (5.96 g, 15.0 mmol) in DMF (100 mL) was added K_2CO_3 (12.34 g, 38.0 mmol) and α,α,α-trifluoromethyl phenol (3.65 g, 22.5 mmol). The solution was stirred ninety degrees Celsius for 28 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford desired aryl ether as an oil (7.54 g, quantitative)

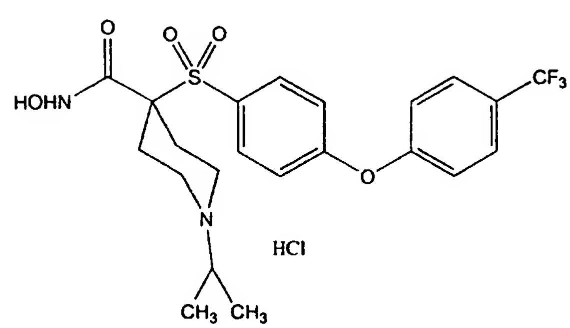
Part B: To a solution of aryl ether from part A (7.54 g, 15.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (6.06 g, 151.0 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=2.0. The resulting precipitate was filtered to give the desired hydrochloride salt as a white solid (7.98 g, quantitative). MS MH^+ calculated for $C_{22}H_{22}NSO_5F_3$: 470, found 470.

Part C: To a solution of the hydrochloride salt of part B (7.60 g, 15.0 mmol) in DMF (100 mL) were added 1-hydroxybenzotriazole (2.44 g, 18.0 mmol), N-methyl morpholine (3.4 mL, 30.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.63 g, 22.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.02 g, 21.0 mmol). The solution was stirred at ambient temperature for 96 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and

dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (5.93g, 69%).

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (3.8 g, 6.7 mmol) in dioxane (100 mL) was added 4 N HCl/dioxane (30 mL). The reaction was stirred at ambient temperature for 2 hours, then the solution was concentrated *in vacuo*. Trituration with diethyl ether afforded the title compound as a white solid (3.33 g, 96%). MS MH^+ calculated for $C_{22}H_{23}N_2SO_5F_3$: 485 , found 485.

Example 428: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]phenyl] sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (30.0 g, 80.8 mmol) in methylene chloride (100 mL) was added trifluoroacetic acid (30 mL) in methylene chloride (40 mL). The solution was stirred at ambient temperature for two hours. The solution

was concentrated *in vacuo*. To the residue dissolved in methylene chloride (150 mL) at zero degrees Celsius were added triethylamine (28.0 mL, 277 mmol), acetone (24.0 mL, 413 mmol), sodium cyanoborohydride (68 g, 323.1 mmol) and acetic acid (18.5 mL, 308 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The solution was diluted with 1N NaOH and extracted with ethyl ether. The organic layer was washed with 1N NaOH, water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to provided the desired isopropylamine (21.03 g, 72%).

Part B: To a solution of the isopropylamine of part A (4.04 g, 11.0 mmol) in DMF (50 mL) was added $CsCO_3$ (10.75g, 33.3 mmol) and α,α,α-trifluoro-p-cresol (2.67g, 16.5 mmol). The solution was stirred at ninety degrees Celsius for 40 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo.* Chromatography on silica gel, eluting with 30% ethyl acetate/hexane, provided the desired diaryl ether as an oil (5.35 g, 97%). HRMS MH^+ calculated for $C_{24}H_{28}NSO_5F_3$: 500.1640, found: 500.1678.

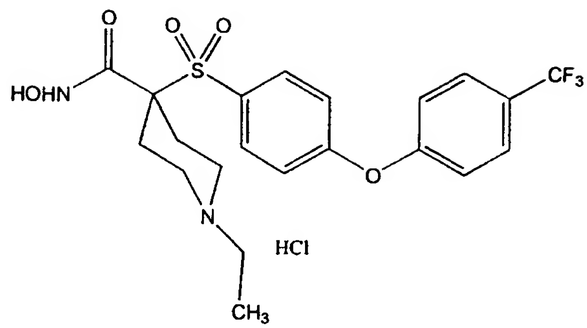
Part C: To a solution of the diaryl ether from part B (5.3 g, 10.6 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (4.2 g, 106.0 mmol) in water (25 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3.0. The resulting precipitate was filtered to give the

desired hydrochloride salt as a white solid (5.38 g, quantitative). MS MH^+ calculated for $C_{22}H_{24}NSO_5F_3$: 472.1406, found 471.472.1407.

Part D: To a solution of the hydrochloride salt of part C (5.4 g, 10.6 mmol) in DMF (90 mL) were added 1-hydroxybenzotriazole (1.72 g, 12.3 mmol), N-methyl morpholine (3.5 mL, 32.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.87 g, 15.9 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.8 g, 15.0 mmol). The solution was stirred at ambient temperature for 144 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with 2% methanol/ethyl acetate, provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (2.74 g, 45%). HRMS MH^+ calculated for $C_{27}H_{33}N_2SO_5F_3$: 571.2090 , found 571.2103

Part E: To a solution of tetrahydropyranyl-protected hydroxamate of part D (2.7 g, 4.7 mmol) in dioxane (50 mL) was added 4 N HCl/dioxane (20 mL). The reaction was stirred at ambient temperature for 2 hours. Filtration afforded the title compound as a white solid (2.08 g, 84%). MS MH^+ calculated for $C_{22}H_{25}N_2SO_5F_3$: 487 , found 487.

Example 429: Preparation of 1-ethyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, <u>monohydrochloride</u>



Part A: To a solution of the product of Example 9, Part D (48 g, 115.0 mmol) in ethyl acetate (750 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 45 minutes, and stirred at that temperature for 7 hours. The solution was concentrated *in vacuo* to afford a residue that was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (32.76 g, 81%).

Part B: To a solution of hydrochloride salt of part A (15.8 g, 45.0 mmol) in DMF (75 mL) was added K_2CO_3 (12.4 g, 90.0 mmol) and bromoethane (3.4 mL, 45.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (200 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the desired ethyl amine as an oil (15.4 g, quantitative).

Part C: To a solution of ethyl amine of part B (5.2 g, 15.0 mmol) in DMF (50 mL) was added $CsCO_3$ (12.21 g, 37.5 mmol) and α,α,α-trifluoro-p-cresol (3.65 g, 23.0 mmol). The solution was stirred ninety degrees Celsius for 25 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water,

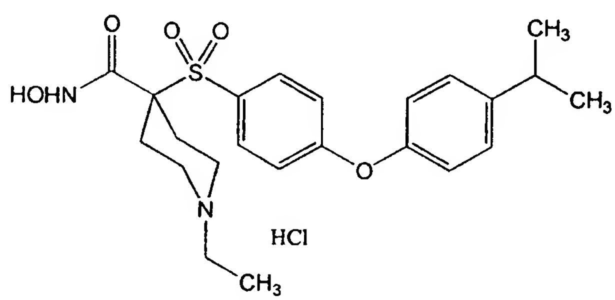
saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with 20% ethyl acetate/hexane, provided the desired diaryl ether as an oil (7.3 g, quantitative yield).

Part D: To a solution of diaryl ether from part C (7.3 g, 15.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (6.0 g, 150 mmol) in water (30 mL), and the solution was heated at sixty degrees Celsius for 16 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=4.0. The resulting precipitate was filtered to give the desired hydrochloride salt as a white solid (5.96 g, 80%). HRMS MH^+ calculated for $C_{21}H_{22}NSO_5F_3$: 458.1249, found 458.1260

Part E: To a solution of the hydrochloride salt of part D (5.96 g, 12.0 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.96 g, 14.0 mmol), N-methyl morpholine (3.9 mL, 36.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.11 g, 18.0 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.24 g, 17.0 mmol). The solution was stirred at ambient temperature for 168 hours. The insoluble material was removed by filtration and the filtrate was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 70% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (2.80 g, 41%).

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (2.8 g, 5.0 mmol) in dioxane (80 mL) was added 4 N HCl/dioxane (20 mL). The reaction was stirred at ambient temperature for 5 hours, and the solution was concentrated *in vacuo*. Trituration with diethyl ether afforded the title compound as a white solid (2.08 g, 84%). MS MH^+ calculated for $C_{21}H_{23}N_2SO_5F_3$: 473, found 473.

Example 430: Preparation of 1-ethyl-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (48 g, 115.0 mmol) in ethyl acetate (750 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 45 minutes. The reaction was stirred at this temperature for 7 hours. The solution was concentrated *in vacuo* to afford a residue which was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (32.8 g, 81%).

Part B: To a solution of the hydrochloride salt of part A (15.8 g, 45.0 mmol) in DMF (75 mL) was added K_2CO_3 (12.4 g, 90.0mmol) and bromoethane (3.4

mL, 45.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (200 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired ethyl amine as an oil (15.4 g, quantitative).

Part C: To a solution of ethyl amine of part B (5.2 g, 15.0 mmol) in DMF (50 mL) was added $CsCO_3$ (12.2 g, 37.5 mmol) and 4-isopropylphenol (3.15 g, 23. 0 mmol). The solution was stirred at ninety degrees Celsius for 5 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo.* Chromatography on silica gel eluting with 20% ethyl acetate/hexane provided the desired diaryl ether as an oil (6.2 g, 95%). HRMS MH^+ calculated for $C_{25}H_{33}N_3SO_5$: 460.2158, found: 460.2160.

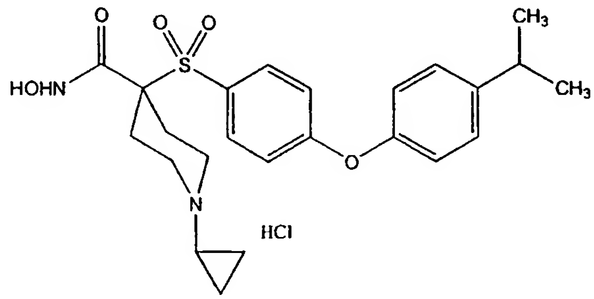
Part D: To a solution of diaryl ether from part C (6.2 g, 13.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (5.2 g, 130 mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 16 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH = 4.0. The resulting precipitate was filtered and washed with H_2O and diethyl ether to give desired hydrochloride salt (6.0 g, quantitative). HRMS MH^+ calculated for $C_{23}H_{29}NSO_5$: 432.1845, found 432.1859.

Part E: To a solution of the hydrochloride salt of part D (6.08 g, 13.0 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (2.11 g, 15.6 mmol), N-

methyl morpholine (4.3 mL, 39.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.28 g, 19.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.49 g, 18.2 mmol). The solution was stirred at ambient temperature for 168 hours. Insoluble material was removed by filtration and the filtrate was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 50% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (1.7 g, 25%). HRMS MH^+ calculated for $C_{28}H_{38}N_2SO_6$: 531.2529, found 531.2537.

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (1.7 g, 3.0 mmol) in dioxane (60 mL) was added 4 N HCl/dioxane (10 mL). The reaction was stirred at ambient temperature for 4 hours, and the solution was concentrated *in vacuo*. Chromatography on C18 reverse phase column eluting with acetonitrile/(HCl)water provided the title compound as a white solid (860 mg, 59%). HRMS MH^+ calculated for $C_{23}H_{30}N_2SO_5$: 447.1954 , found 447. 1972

Example 431: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy] phenyl]-sulfonyl]-4-piperidine-carboxamide, monohydrochloride



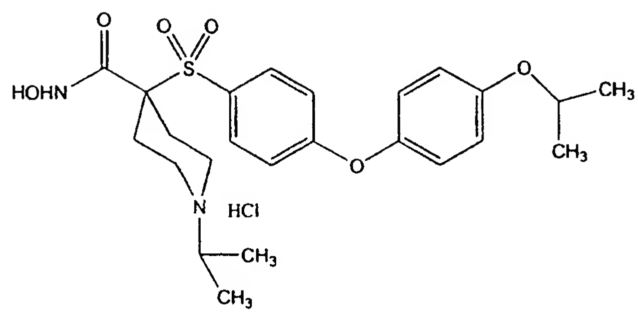
Part A: To a solution of the product of Example 398, Part A (4.0 g, 10.2 mmol) in DMF (40 mL) was added K_2CO_3 (12.46 g, 38.0 mmol) and 4-isopropylphenol (4.99 g, 15.3 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica eluting with 30% ethyl acetate/hexane provided the desired diaryl ether as a white solid (3.89g, 76%). HRMS MH^+ calculated for $C_{26}H_{33}NSO_5$: 472.2158, found: 472.2171.

Part B: To a solution of diaryl ether from part A (3.89 g, 8.20 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (3.30 g, 82.5 mmol) in water (25 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* to remove most of the organic solvents and the aqueous residue was acidified to pH=3.0. The resulting precipitate was filtered and washed with H_2O and ethyl ether to give desired hydrochloride salt (7.98 g, quantitative) as a white solid. MS MH^+ calculated for $C_{24}H_{29}NSO_5$: 444, found: 444.

Part C: To a solution of the hydrochloride salt of part B (3.6 g, 7.0 mmol) in DMF (70 mL) were added 1-hydroxybenzotriazole (1.22 g, 9.0 mmol), N-methyl morpholine (2.3 mL, 21.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.23 g, 10.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.01 g, 10.4 mmol). The solution was stirred at ambient temperature for 15 days. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with 15% ethyl acetate/hexane, provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (3.51 g, 92%). HRMS MH^+ calculated for $C_{29}H_{38}N_2SO_6$: 543.2529, found 543.2539.

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (3.51 g, 6.0 mmol) in methanol (10 mL) and dioxane (200 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated *in vacuo*. Trituration with diethyl ether afforded the title compound as a white solid (2.56 g, 86%). MS MH^+ calculated for $C_{24}H_{30}N_2SO_5$: 459.1875, found 459.1978.

Example 432: Preparation of N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]phenyl]sulfonyl]-1-(1-methylethyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(1-methylethyl)-4-piperidinecarboxylate (2.0 g, 5.4 mmol) in N,N-dimethylformamide (10 mL) was added 4-isopropyloxyphenol, which may be prepared according to the procedure of *J. Indian Chem. Soc.*, 73, 1996, 507-511, (1.63 g, 10.7 mmol) and cesium carbonate (7 g, 21.5 mmol) and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane to afford the desired aryl ether (1.06 g, 39%).

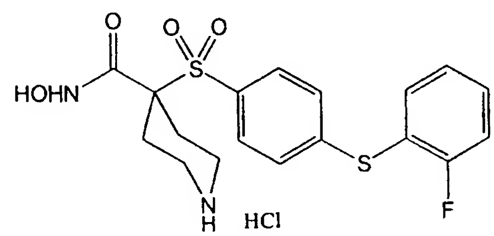
Part B: To a solution of the aryl ether (1.06 g, 2.1 mmol) in ethanol (20 mL) and water (20 mL) was added sodium hydroxide (0.84 g, 21 mmol) and the mixture was heated to 65 degrees Celsius for 16

hours. The solvents were then removed *in vacuo*. Water (50 mL) was added and the mixture was again concentrated *in vacuo* and the resulting mixture was acidified with 2 N HCl to pH=4-5. The solid precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (3.13 g, 100%).

Part C: A solution of the carboxylic acid of part B (1.0 g, 2.0 mmol) in thionyl chloride (5 mL) was refluxed for 2 hours . The solvent was removed *in vacuo*. To the resulting residue in DMF (10 mL) was added N-methyl morpholine (0.66 mL, 6.0 mmol)) and O-tetrahydropyranyl hydroxyl amine hydrochloride (351 mg, 3.0 mmol). The solution was stirred at ambient temperature for 18 hours. The suspension was filtered and the filtrate was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 90% ethyl acetate/hexane provided the desired tetrahydropyran-protected hydroxamate as a white solid (280 mg, 23%). HRMS MH^+ calculated for $C_{29}H_{40}N_2SO_7$: 561.2634, found 561.2653.

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (275 mg, 0.48 mmol) in dioxane (15 mL) was added 4 N HCl/dioxane (5 mL). After stirring at ambient temperature for 2 hours, the solution was concentrated *in vacuo*. Trituration with diethyl ether and filtration of the resulting solid gave the title compound as a white solid (193 mg, 76%). MS MH^+ calculated for $C_{24}H_{32}N_2SO_6$: 477, found 477.

Example 433: Preparation of 4-[[4-[(2-fluorophenyl)-thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (6.0 g, 14.4 mmol) in N,N-dimethylformamide (30 mL) were added 2-fluorothiophenol (2.22 g, 17.3 mmol) and potassium carbonate (2.40 g, 17.3 mmol), and the resulting suspension was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with ethyl acetate (200 mL) and washed with 1 N sodium hydroxide (200 mL) and brine (3X). Concentration of the organic phase afforded a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:4), to afford the desired aryl sulfide (8.0 grams, 100%) as a white solid.

Part B: To a solution of the ethyl ester of part A (8.0 g, 15 mmol) in ethanol (90 mL) and water (20 mL) was added sodium hydroxide (6.1 g, 152 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Volatile organics were removed *in vacuo* and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with

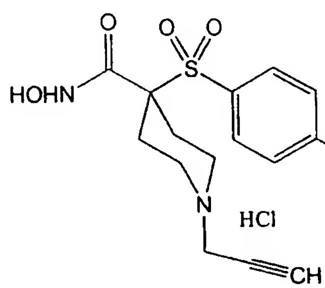
ethyl acetate. The combined organic extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (4.92 g, 68%).

Part C: To a solution of the carboxylic acid of part B (4.92 g, 9.93 mmol) in N,N-dimethylformamide (100 mL) were added 4-methylmorpholine (1.52 g, 15.0 mmol), N-hydroxybenzotriazole (1.62 g, 12.0 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.70 g, 14.1 mmol), followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (2.24 g, 15.0 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel afforded the protected hydroxamate derivative (4.9 mg, 83%).

Part D: Hydrogen chloride gas was bubbled for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C (4.9 g, 8.24 mmol) in ethyl acetate (30 mL). The mixture was then allowed to stand at ambient temperature for 2 hours, after which time the solvent was removed *in vacuo*. Fresh ethyl acetate (30 mL) was added and then removed *in vacuo*, and this procedure was repeated. Ethyl acetate (50 mL) was then added and the solid was collected by filtration to afford a solid that was purified by reverse-phase chromatography,, eluting with acetonitrile/water (gradient of 20/80 up to 100% acetonitrile), to afford the title compound (1.9 g, 43%). Analytical calculation for

$C_{18}H_{19}FN_2O_4S_2$.HCl: C, 48.37; H, 4.51; N, 6.27; Cl, 7.93. Found: C, 48.14; H, 4.33; N, 6.21; Cl, 8.64. HRMS (ESI) MH^+ calculated for $C_{18}H_{19}FN_2O_4S_2$: 411.0849, found 411.0844.

Example 434: Preparation of 4-[[4-[(2-fluorophenyl)-thio]phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part F (4.46 g, 12.6 mmol) in N,N-dimethylformamide (30 mL) were added 2-fluorothiophenol (1.94 g, 15.1 mmol) and potassium carbonate (2.09 g, 15.1 mmol), and the resulting suspension was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with ethyl acetate (200 mL) and washed with 1 N sodium hydroxide (200 mL) and brine (3X). Concentration of the organic phase afforded the desired aryl sulfide (5.2 grams, 90%).

Part B: To a solution of the ethyl ester of part A (5.1 g, 11.4 mmol) in ethanol (90 mL) and water (30 mL) was added sodium hydroxide (5.0 g, 125 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Organics were removed *in vacuo*

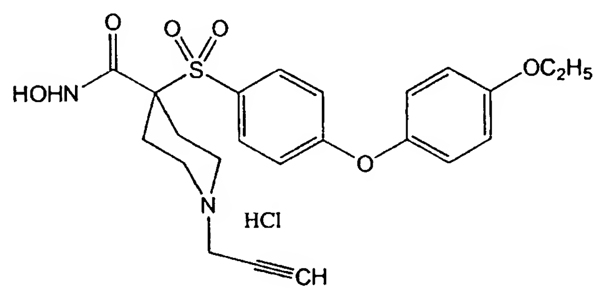
and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (4.5 g, 94%).

Part C: To a solution of the carboxylic acid of part B (4.5 g, 11.0 mmol) in N,N-dimethylformamide (50 mL) were added 4-methylmorpholine (1.62 g, 16.0 mmol), N-hydroxybenzotriazole (1.73 g, 12.8 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.87 g, 14.9 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (2.39 g, 16.0 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel afforded the protected hydroxamate derivative that was used directly in the next step.

Part D: Hydrogen chloride gas was bubbled for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C in ethyl acetate (30 mL). The mixture was then allowed to stand at ambient temperature for 2 hours after which time the solvent was removed *in vacuo*. Fresh ethyl acetate (30 mL) was added and then removed *in vacuo*, and this procedure was repeated. Ethyl acetate (50 mL) was then added and the solid was collected by filtration to afford a solid which was purified by reverse-phase chromatography eluting with acetonitrile/water

(gradient of 20/80 up to 100% acetonitrile) to afford the title compound (1.85 g, 35% for parts C and D). HRMS (ESI) MH^+ calculated for $C_{21}H_{21}FN_2O_4S_2$: 449.1005, found 449.1023.

Example 435: Preparation of 4-[[4-(4-ethoxyphenoxy)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part F (8.00 g, 22.6 mmol) in N,N-dimethylformamide (50 mL) were added 4-ethoxyphenol (9.38 g, 70 mmol) and cesium carbonate (22.8 g, 70 mmol), and the resulting suspension was heated at 75 degrees Celsius for 20 hours. The reaction mixture was then diluted with ethyl acetate (1000 mL) and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:2), to afford the desired diaryl ether (10.5 grams, 99%).

Part B: To a solution of the ethyl ester of part A (10.5 g, 22.3 mmol) in ethanol (70 mL) and water (60 mL) was added sodium hydroxide (8.9 g, 222 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Volatile organics were removed

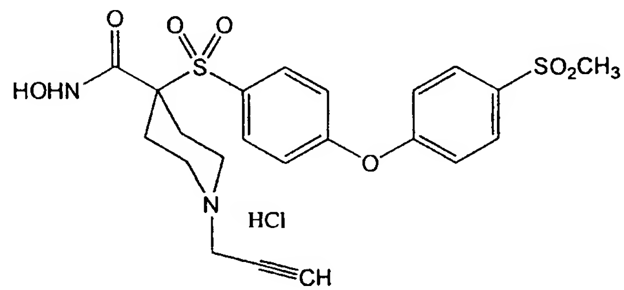
in vacuo and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (10 g, 100%).

Part C: To a solution of the carboxylic acid of part B (10 g, 22.5 mmol) in N,N-dimethylformamide (50 mL) were added 4-methylmorpholine (3.42 g, 33.8 mmol), N-hydroxybenzotriazole (3.66 g, 27.1 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.05 g, 31.6 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (5.05 g, 33.8 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane (1:1), afforded the protected hydroxamate derivative (6.5 g, 53%) which was used directly in the next step.

Part D: To a solution of the protected hydroxamate of part C in methanol/1,4-dioxane (1:3, 70 mL) was added 4 N HCl/1,4-dioxane (30 mL) and the solution was stirred at ambient temperature for 4 hours. The solvent was then removed *in vacuo*. Methanol (40 mL) was added and then removed *in vacuo*. Diethyl ether (100 mL) was added and the resulting solid was collected by filtration to afford the title compound (4.3 g, 72%). Analytical calculation for $C_{23}H_{26}N_2O_6S.HCl.H_2O$: C, 53.85; H, 5.70; N, 5.46; Cl,

6.91; S, 6.25. Found: C, 53.65; H, 5.62; N, 5.41; Cl, 6.86; S, 6.48. MS (ESI) MH^+ calculated for $C_{23}H_{26}N_2O_6S$: 459, found 459.

Example 436: Preparation of N-hydroxy-4-[[4-[4-(methylsulfonyl)phenoxy]phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part F (2.5 g, 6.4 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylsulphonylphenol (3.5 g, 20.3 mmol) and cesium carbonate (8.7 g, 27 mmol), and the resulting suspension was heated at 90 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500 mL) and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to afford the desired aryl ether (2.5 grams, 77%).

Part B: To a solution of the ethyl ester of part A (2.5 g, 4.9 mmol) in ethanol (50 mL) and water (30 mL) was added sodium hydroxide (2.0 g, 49 mmol) and the mixture was heated to 65 degrees

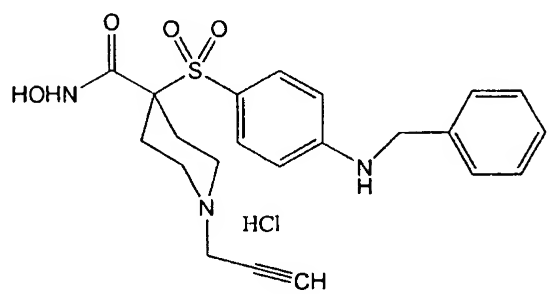
Celsius for 8 hours. The solvents were removed *in vacuo*. Water (50 mL) was added, the mixture was again concentrated *in vacuo* and the resulting mixture was acidified with 2 N HCl to pH=4-5. The solid precipitate was collected by filtration to afford the desired carboxylic acid (1.57 g, 67%).

Part C: To a solution of the carboxylic acid of part B (1.57 g, 3.3 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.5 g, 4.9 mmol), N-hydroxybenzotriazole (0.53 g, 3.9 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.88 g, 4.6 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.74, 4.9 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (1.5 g, 79%), which was used directly in the next step.

Part D: To a solution of the protected hydroxamate of part C (1.5 g, 2.60 mmol) in methanol/1,4-dioxane (1:3, 40 mL) was added 4 N HCl/1,4-dioxane (10 mL), and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. Methanol (30 mL) was added and then removed *in vacuo*. Diethyl ether (100 mL) was added and the resulting solid was collected by filtration to afford the title compound (1.35 g, 98%). Analytical calculated for $C_{22}H_{24}N_2O_7S_2.HCl$: C, 49.95; H, 4.76; N, 5.30; Cl, 6.70; S, 12.12. Found:

C, 49.78; H, 4.56; N, 5.25; Cl, 6.98; S, 11.98. HRMS (ESI) MH_+ calculated for $C_{22}H_{24}N_2O_7S_2$: 493.1103, found 493.1116.

Example 437: Preparation of N-hydroxy-4-[[4-[(phenylmethyl)amino]phenyl]sulfonyl]-1-(2-propynyl-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part F (2.5 g, 6.4 mmol) in N,N-dimethylformamide (30 mL) were added benzylamine (3.44 g, 32.1 mmol) and cesium carbonate (10.5 g, 32.3 mmol) and the resulting suspension was heated at 100 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500 mL) and washed with water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:1), to afford the desired benzyl aniline derivative (2.5 grams, 88%).

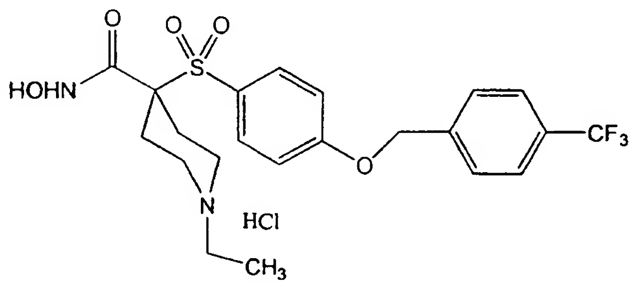
Part B: To a solution of the ethyl ester of part A (2.5 g, 5.67 mmol) in ethanol (50 mL) and water (30 mL) was added sodium hydroxide (2.27 g, 56.7 mmol), and the mixture was heated to 65 degrees

Celsius for 8 hours. The solvents were removed *in vacuo*. Water (50 mL) was added and the mixture was again concentrated *in vacuo* and the resulting mixture was acidified with 2 N HCl to pH = 4-5. The solid precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (2.3 g, 98%).

Part C: To a solution of the carboxylic acid of part B (2.3 g, 5.57 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.85 g, 8.36 mmol), N-hydroxybenzotriazole (0.9 g, 6.69 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 g, 7.8 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.25, 8.36 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue which was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the next step.

Part D: Hydrogen chloride gas was bubbled for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C in ethyl acetate (50 mL). The solvent was then removed *in vacuo*. Ethyl acetate (100 mL) was added and then removed *in vacuo*. Ethyl acetate (100 mL) was then added and the resulting solid was collected by filtration to afford the title compound (1.6 g, 62% for steps C and D). HRMS (ESI) MH^+ calculated for $C_{22}H_{25}N_3O_4S$: 428.1644, found 428.1652.

Example 438: Preparation of 1-ethyl-N-hydroxy-4-[[4-[[4-[trifluoromethyl)phenyl]methoxy]-phenyl]sulfonyl]-4-piperidine-carboxamide, monohydrochloride



Part A: To a solution of the product of Example 429, Part B (1.0 g, 2.9 mmol) in N,N-dimethylacetamide (30 mL) were added 4-(trifluoromethyl)benzyl alcohol (1.53 g, 8.74 mmol) and cesium carbonate (2.85 g, 8.74 mmol), and the resulting suspension was heated at 95-100 degrees Celsius for 8 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel eluting with ethyl acetate/hexane to afford the desired aryl ether (0.8 grams, 54%).

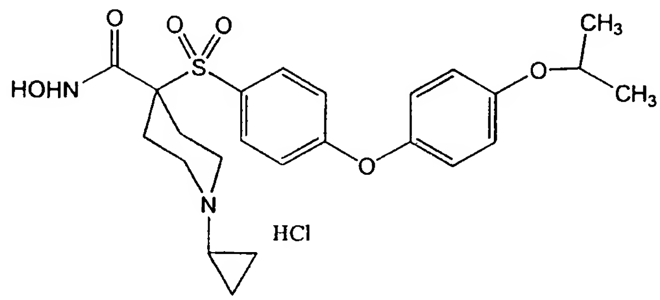
Part B: To a solution of the ethyl ester of part A (0.8 g, 1.5 mmol) in ethanol (50 mL) and water (50 mL) was added sodium hydroxide (1.0 g, 25 mmol) and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed *in vacuo*. Water (50 mL) was added and the mixture was acidified with 2 N HCl to pH=4. The solid

precipitate was collected by filtration to afford the desired carboxylic acid (0.75 g, 99%).

Part C: To a solution of the carboxylic acid of part B (0.75 g, 1.54 mmol) in N,N-dimethylformamide (10 mL) were added 4-methylmorpholine (0.47 g, 4.6 mmol), N-hydroxybenzotriazole (0.25 g, 1.85 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.41 g, 2.16 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.35, 2.3 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (250 mg, 57%).

Part D: To a solution of the protected hydroxamate of part C (250 mg, 0.43 mmol) in methanol/1,4-dioxane (1:3, 20 mL) was added 4 N HCl/1,4-dioxane (5 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. An additional portion of ethyl acetate was added and then removed *in vacuo*. Diethyl ether (100 mL) was added and the resulting solid was collected by filtration to afford the title compound (190 mg, 82%). MS (CI) MH^+ calculated for $C_{22}H_{25}F_3N_2O_5S$: 487, found 487.

Example 439: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]-phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 398, Part A (2.49 g, 7.0 mmol) in N,N-dimethylacetamide (30 mL) were added 4-isopropoxyphenol, which may be prepared according to the procedure of *J. Indian Chem. Soc.* 73, 1996, 507-511,(1.28 g, 8.4 mmol) and cesium carbonate (5.48 g, 16.8 mmol), and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired aryl ether (2.8 grams, 82%).

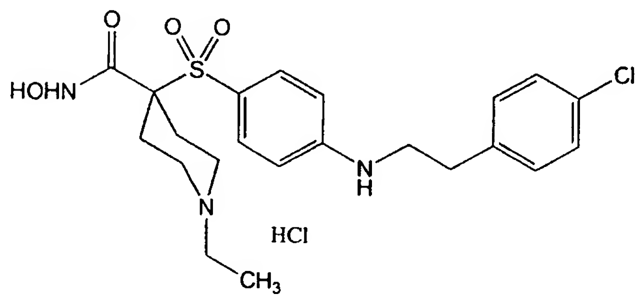
Part B: To a solution of the ethyl ester of part A (2.8 g, 5.7 mmol) in ethanol (50 mL) and water (50 mL) was added sodium hydroxide (2.3 g, 57 mmol) and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed *in*

vacuo. Water (50 mL) was added and the mixture was acidified with 2 N HCl to pH = 4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (1.4 g, 53%).

Part C: To a solution of the carboxylic acid of part B (1.4 g, 3.1 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.92 g, 9.1 mmol), N-hydroxybenzotriazole (0.49 g, 3.66 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.82 g, 4.26 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.68 g, 4.5 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the next step.

Part D: To a solution of the protected hydroxamate from part C in methanol/1,4-dioxane (1:3, 20 mL) was added 4 N HCl/1,4-dioxane (10 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. An additional portion of ethyl acetate was added and then removed *in vacuo*. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (0.3 g, 19% for parts C and D together). Analytical calculation for $C_{24}H_{30}N_2O_6S.HCl$: C, 56.41; H, 6.11; N, 5.48. Found: C, 56.04; H, 5.82; N, 5.44. MS (CI) MH+ calculated for $C_{24}H_{30}N_2O_6S$: 475, found 475.

Example 440: Preparation of 4-[[4-[[2-(4-chlorophenyl)-ethyl]amino]phenyl]-sulfonyl]-1-ethyl-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 429, Part B (1.0 g, 2.91 mmol) in N,N-dimethylacetamide (20 mL) were added 4-chlorophenethylamine (0.91 g, 5.8 mmol) and cesium carbonate (3.80 g, 11.6 mmol), and the resulting suspension was heated at 90 degrees Celsius for 24 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane to afford the desired aryl ether (0.8 grams, 58%).

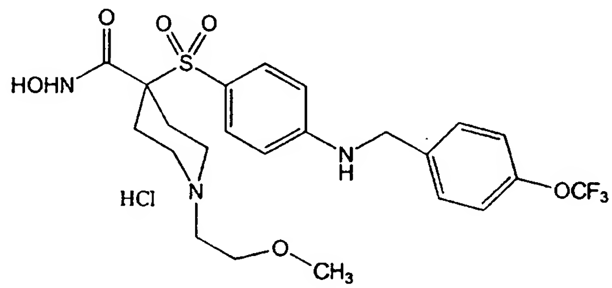
Part B: To a solution of the ethyl ester of part A (0.8 g, 1.7 mmol) in ethanol (50 mL) and water (50 mL) was added sodium hydroxide (1.0 g, 25 mmol), and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed *in vacuo*. Water (50 mL) was added and the mixture was

acidified with 2 N HCl to pH=4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (0.75 g, 92%).

Part C: To a solution of the carboxylic acid of part B (0.75 g, 1.7 mmol) in N,N-dimethylformamide (20 mL) were added 4-methylmorpholine (0.51 g, 5.1 mmol), N-hydroxybenzotriazole (0.27 g, 2.0 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.45 g, 2.3 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.37 g, 2.5 mmol). After stirring for 16 hours at ambient temperature the reaction mixture was concentrated to a residue which was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the next step.

Part D: To a solution of the protected hydroxamate from part C in methanol/1,4-dioxane was added 4 N HCl/1,4-dioxane (10 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. An additional portion of ethyl acetate was added and then removed *in vacuo*. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (30 mg, 4% for parts C and D together).

Example 441 Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[[4-(trifluoromethoxy)phenyl]methyl]amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.38g, 3.7 mmol) in N,N-dimethylformamide (20 mL) were added 4-(trifluoromethyloxy)benzylamine (1.0 g, 5.2 mmol) and cesium carbonate (1.7 g, 5.2 mmol), and the resulting suspension was heated at 90 degrees Celsius for 24 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired trifluoromethoxy compound (0.6 grams, 30%).

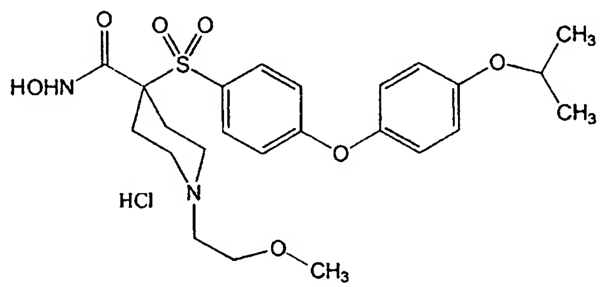
Part B: To a solution of the ethyl ester of part A (0.6 g, 1.1 mmol) in ethanol (30 mL), water (30 mL) and tetrahydrofuran (15 mL) was added sodium hydroxide (0.44 g, 11 mmol), and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed *in vacuo*. Water (50 mL) was

added and the mixture was acidified with 2 N HCl to pH=4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (0.5 g, 88%).

Part C: To a solution of the carboxylic acid of part B (0.50 g, 0.98 mmol) in N,N-dimethylformamide (10 mL) were added 4-methylmorpholine (0.15 g, 1.5 mmol), N-hydroxybenzotriazole (0.16 g, 1.2 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.27 g, 1.4 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.22 g, 1.5 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (110 mg, 18%).

Part D: To a solution of the protected hydroxamate from part C (110 mg, 0.18 mmol) in methanol/1,4-dioxane (1:4, 20 mL) was added 4 N HCl/1,4-dioxane (7 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. An additional portion of methanol (20 mL) was added and then removed *in vacuo*. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (30 mg, 31%). MS (ESI) MH^+ calculated for $C_{23}H_{28}F_3N_3O_6S$: 532, found 532.

Example 442: Preparation of N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]phenyl]sulfonyl]-1-(2-methoxyethyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenyl-sulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (2.0 g, 5.4 mmol) in N,N-dimethylformamide (20 mL) were added 4-isopropoxyphenol, which can be prepared according to the procedure of *J. Indian Chem. Soc.* 73, 1996, 507-511, (1.63 g, 10.7 mmol) and cesium carbonate (7 g, 21.5 mmol), and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired aryl ether (1.37 grams, 50%).

Part B: To a solution of the ethyl ester of part A (1.37 g, 2.7 mmol) in ethanol (30 mL) and water (30 mL) was added sodium hydroxide (1.08 g, 27

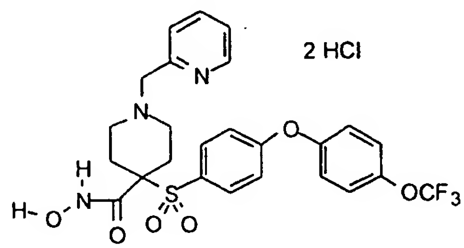
mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. The solvents were then removed *in vacuo*. Water (50 mL) was added and the mixture was again concentrated *in vacuo* and the resulting mixture was acidified with 2 N HCl to pH = 4-5. The solid precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (1.25 g, 100%).

Part C: To a suspension of the carboxylic acid of part B (1.25 g, 2.7 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.82 g, 8.1 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.61, 4.1 mmol) followed by bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP, 1.51 g, 3.3 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate and washed with water and brine Concentration and purification by chromatography on silica, gel eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (1.0 g, 63%).

Part D: Hydrogen chloride gas was bubbled for 5 minutes through an ice bath-cooled solution of the protected hydroxamate of part C (1.0 g, 1.7 mmol) in ethyl acetate (20 mL). After stirring at ambient temperature for 5 hours, the solvent was removed *in vacuo*. Ethyl acetate (30 mL) was added and then removed *in vacuo*. Ethyl acetate (30 mL) was again added and the resulting solid was collected by filtration to afford the title compound (0.5 g, 56%). Analytical calculation for $C_{24}H_{32}N_2O_7S \cdot HCl \cdot 1.5H_2O$: C, 51.84; H, 6.53; N, 5.04; Cl, 6.38; S, 5.77. Found:

C, 51.87; H, 6.12; N, 4.92; Cl, 6.38; S, 5.84. MS MH^+ calculated for $C_{24}H_{32}N_2O_7S$: 493, found 493.

Example 443: Preparation of N-Hydroxy-1-(2-pyridinylmethyl)-4-[4-(4-trifluoro-methoxyphenoxy)phenyl]sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: The aryl flouride from Example 9, Part D (6.22 g, 15 mmol) was combined with powdered potassium carbonate (3.04 g, 22 mmol), 4-(trifluoromethoxy)phenol (3.92 g, 322 mmol), and N,N-dimethylforamide (7 mL), and the mixture was stirred at ninety degrees Celcius for sixteen hours. Additional 4-(trifluoromethoxy)-phenol (1 g) and potassium carbonate (800 mg) were added and the reaction was continued at one hundred and fifteen degrees Celsius for twenty additional hours. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL, then 2 X 25 mL). The combined organic layers were dried using magnesium sulfate, concentrated, and chromatographed, affording the desired aryl ether as an oil (9.6 g, about quantitative).

Part B: The aryl ether from part A (9.6 g, about 15 mmol) was dissolved in ethyl acetate (45

mL). A solution of HCl in dioxane (4N, 12 mL) was added, and the mixture was stirred at ambient temperature for three hours. Thin layer chromatography indicated incomplete deprotection. Concentrated aqueous HCl (4 mL) was added and the reaction was heated to reflux with a heat gun several times. The solution was concentrated and was then azeotroped with acetonitrile to afford the desired piperidine hydrochloride salt as a foam (9.6 g). Nuclear magnetic resonance spectroscopy indicated some contaminating 4-(trifluoromethoxy)phenol, which must have been carried through from part A.

The piperidine hydrochloride salt (6.0 g) was dissolved in ethyl acetate (125 mL) and washed with aqueous sodium hydroxide (2 g NaOH in 50 mL water). The organic layer was dried with magnesium sulfate and filtered through a pad of silica gel. The phenol contaminant was eluted. The desired piperidine was then freed from the filter cake by elution with methanol containing 1% aqueous ammonium hydroxide (circa 100 mL). The filtrate was concentrated and azeotroped with acetonitrile to yield 3.3 g (7.3 mmol).

Part C: The piperidine from Part B (1.24 g, 2.7 mmol) was combined with powdered potassium carbonate (828 mg, 6.0 mmol), 2-picolyl hydrochloride (492 mg, 3.0 mmol), and N,N-dimethylformamide (3 mL), and the mixture was stirred at ambient temperature for two hours, then heated at fifty degrees Celsius for two additional hours. The mixture was diluted with water (40 mL) and extracted with ethyl acetate (150 mL, then 50 mL). The combined organic layers were dried using magnesium sulfate, concentrated, and

chromatographed, affording the desired ester as an oil (1.13 g, 74%).

Part D: The ester from part C (1.1 g, 2.0 mmol) was combined with ethanol (6 mL), water (2 mL), and potassium hydroxide (0.90 g, 16 mmol). The mixture was brought to reflux and heated for four and one-half hours. The solution was then cooled to zero degrees Celsius and acidified using concentrated aqueous hydrogen chloride. The solvent was removed, and the resulting solids were dried by azeotroping with acetonitrile. A vacuum was applied until constant weight was achieved.

The crude acid hydrochloride salt was stirred with N-methylmorpholine (about 0.5 mL), 1-hydroxybenzotriazole (0.405 g, 3 mmol), O-tetrahydropyranyl hydroxylamine (0.35 g, 3.0 mmol), and N,N-dimethyformamide (9 mL). After ten minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.57 g, 3.0 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous sodium bicarbonate (50 mL), and extracted with ethyl acetate (100 mL, then 25 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed (9:1 ethyl acetate: methanol) to afford the desired tetrahydropyranyl-protected hydroxamate as a yellow oil (1.20 g, 95%).

Part E: The tetrahydropyranyl-protected hydroxamate (1.20 g, 1.90 mmol) was diluted with methanol (9 mL). Acetyl chloride (0.78 mL, 11 mmol) was added over two minutes. The reaction was stirred for 2 hours at ambient temperature, then concentrated to afford the desired dihydrochloride salt (1.20 g,

quantitative yield) as a white crystalline solid. Anaytical calculation for $C_{25}H_{24}F_3N_3O_6S.2HCl.1/3\ H_2O$: C, 47.58; H, 4.07; N, 6.66. Found: C, 47.31; H, 4.14; N, 6.80.

Example 444: *In Vitro* Metalloprotease Inhibition

The compounds prepared in the manner described in the Examples above were assayed for activity by an *in vitro* assay. Following the procedures of Knight et al., *FEBS Lett.* 296(3):263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin-activated MMPs were incubated with various concentrations of the inhibitor compound at room temperature for 5 minutes.

More specifically, recombinant human MMP-13, MMP-1, MMP-2 and MMP-9 enzymes were prepared in laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a baculovirus as discussed in V.A. Luckow, Insect Cell Expression Technology, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, 67:4566-4579 (1993); O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al., The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992) for further details on use of baculovirus expression systems. The expressed enzyme was purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay.

MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr. Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Further specifics for preparation and use of these enzymes can be found in the scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, Ca (1992) and the citations therein, and Frije et al., J. Biol. Chem., 26(24): 16766-16773 (1994). The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

MCA-ProLeuGlyLeuDpaAlaArgNH_2, wherein MCA is methoxycoumarin and Dpa is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine. This substrate is commercially available from Baychem as product M-1895.

The buffer used for assays contained 100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$ and 0.05 percent polyethyleneglycol (23) lauryl ether at a pH value of 7.5. Assays were carried out at room temperature, and dimethyl sulfoxide (DMSO) at a final concentration of 1 percent was used to dissolve inhibitor compound.

The assayed inhibitor compound in DMSO/buffer solution was compared to an equal amount of DMSO/buffer with no inhibitor as control using Microfluor™ White Plates (Dynatech). The inhibitor or control solution was maintained in the plate for 10 minutes and the substrate was added to provide a final concentration of 4 μM.

In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the gly-leu peptide bond, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescence intensity (excitation at 328 nm/emission at 415 nm). Inhibition was measured as a reduction in fluorescent intensity as a function of inhibitor concentration, using a Perkin Elmer L550 plate reader. The IC_{50} values were calculated from those values. The results are set forth in the Inhibition Tables A and B below, reported in terms of IC_{50} to three significant figures, where appropriate.

Inhibition Table A (nM)

Example Number	MMP-13 IC_{50} (nM)	MMP-2 IC_{50} (nM)	MMP-1 IC_{50} (nM)	MMP-9 IC_{50} (nM)
1	5.1	2.6	6600	31.6
2	0.25	0.1	220	1.4
3	0.3	0.2	1140	
4	0.35	0.23	1090	5
5	4800	1800	>10000	
6	0.25	0.15	327	
7	37.2	1.8	>10000	235

8	24.1	4	>10000	290
9	0.5	0.2	9000	1.5
10	0.4	0.2	1600	0.3
11	6	4.4	>10000	
12	<0.1	<0.1	464	
13	0.6	0.4	>10000	8
14	0.1	<0.1	464	
15	0.4	0.2	3600	0.2
16	2.4	100	>10000	2500
17	0.3	0.2	400	0.3
18	0.5	0.3	800	
19	9	13.9	>10000	
20	1.7	23.5	10000	
21	0.6	1.3	>10000	
22	1.2	0.9	>10000	
23	0.2	<0.1	2275	
24	0.4	1	>10000	3.7
25	3	2.6	>10000	
26	0.5	0.2	7700	7
27	0.45	0.4	>10000	4
28	<0.1	<0.1	770	
29	0.3	0.15	>10,000	

Inhibition Table B (nM)

Example Number	MMP-1 IC_{50} (nM)	MMP-2 IC_{50} (nM)	MMP-9 IC_{50} (nM)	MMP-13 IC_{50} (nM)
30	350	0.1	0.3	0.1
31	370	<0.1		0.2
32	>10000	0.1	2.5	0.2
33	>10000	0.5	9.4	0.8

34	>10000	1.1		1.2
35	>10000	0.3	3	0.5
36	7300	0.4	8	0.6
37	1000	0.2		0.3
38	>10000	20	135	22
39	>10000	230		24.5
40	4400	0.4	2.4	1.9
41	1200	0.15		0.2
42	2200	0.2	1.3	0.4
43	7000	0.4		0.8
44a	>10000	<0.1		0.2
44b	>10000	8000		>10000
45	8800	2.5		1.7
46	710000	—	—	710000
47a	>10000	7		14.6
47b	>10000	3000		3100
48	210	0.2		0.25
49	>10000	76.9		90.0
51	5500	0.7		1.3
52	>10000	2.7		5.9
53	>10000	0.3	92	1.5
54	>10000	60		120
55	1200	0.1		0.3
56	1500	<0.1		0.15
57	1200	<0.1		0.2
58	>10000	83		30
59	>10000	130		180
60	>10000	64		147
61	>10000	1500		2000
62	>10000	>10000		>10000
63	>10000	18.1	530	1.5
64	1470	<0.1		0.15

65	8000	0.6	4.4	0.7
66	>10000	4590		36000
67	1600	239		268
68	>10000	5.3	130	6
69	1140	<0.1	0.2	<0.1
70	1500	0.2	7.3	0.8
71	3600	0.35	5	0.8
72	2100	<0.1		0.3
73	1140	<0.1	0.2	<0.1
74	>10000	130		480
75	>10000	60		900
78	>10000	6	50	10
79	>10000	1		1.7
80	3000	0.1	1.8	0.2
81	3300	0.1		0.3
82	4000	0.1		0.3
83	8000	1.2	5	1.5
84	8000	1.8		2.5
85	500	<0.1	0.4	<0.1
86	>10000	2.5		3.5
87	7200	0.8	13.9	0.35
88	1100	0.2	0.5	0.2
89	1200	0.15	0.4	0.25
90	1200	0.1		0.1
91	1800	1.5	40	2.1
92	>10000	1800		2430
93	8000	0.4	3.5	0.7
94	268	<0.1	0.4	<0.1
95	>10000	1	3.6	0.5
96	5000	0.2	1.3	0.3
97	4000	8.2		16.7
98	>10000	37		23.4

99	>10000	0.4		1
100	435	<0.1	0.3	0.15
101	1800	0.3	2.9	0.45
102	2000	<0.1		0.2
103	>10000	0.8	10	0.7
104	>10000	1.5	42.8	0.65
105	>10000	3500	114	0.85
106	>10000	27.1		12.1
107	>10000	12.1		6
108	2000	0.4		0.4
109	500	0.1	0.7	0.3
110	2700	0.4	10	0.5
111	3700	0.5		1.3
112	1000	7		3.2
113	>10000	0.9		4
114	3000	0.65	31.6	0.4
115	4500	0.3	31.6	0.6
116	2350	2	15.3	5.5
117	3700	0.6	45.4	4.8
118	2850	0.3	50	0.8
119	>10000	1.5	30	1.7
120	4000	0.4		0.4
121	1200	<0.1		0.2
122	600	0.1		0.15
123	3600	1.8	27.8	1.8
124	1000	0.5		1.1
125	>10000	0.4	7	0.5
126	8000	11.3		10
127	>10000	37		40
128	>10000	23.8		20
129	>10000	>100		1000
130	>10000	57.7		45.9

131	>10000	650	10
132	>10000	420	
133	>10000	90	27
134	9000	29	4
135	>10000	500	65
136	>10000	445	40
137	>10000	300	34.7
138	>10000	>100	>100
139	>10000	1000	25.4
140	>10000	1000	60
141	>10000	>100	>100
142	>10000	600	70
143	>10000	900	23.9
144	>10000	800	30.7
145	>10000	>100	>100
146	>10000	650	32.6
147	>10000	2700	31
148	>10000	2400	31
149	>10000	1600	15.5
150	>10000	1300	14.5
151	>10000	1500	35
152	>10000	2400	16.5
153	>10000	2700	13.5
154	>10000	1600	27
155	>10000	>1000	>100
156	>10000	3300	27.8
157	>10000	6000	90
158	>10000	5000	80
159	>10000	2500	15.6
160	>10000	4700	33.7
161	>10000	>1000	>100
162	>10000	>1000	>100

163	>10000	4000	77.4
164	>10000	1750	20
165	>10000	330	13.6
166	>10000	>1000	>100
167	>10000	>1000	>100
168	>10000	>1000	>100
169	10000	>1000	>100
170	10000	>1000	>100
171	>10000	>1000	>100
172	>10000	>1000	>100
173	>10000	>1000	>100
174	8000	900	>100
175	10000	>1000	>100
176	>10000	400	25
177	>10000	400	21
178	>10000	540	>100
179	>10000	440	100
180	5000	128	4
181	10000	121	6.1
182	>10000	240	4
183	>10000	288	40
184	>10000	94	7
185	>10000	210	17.5
186	>10000	120	10
187	>10000	290	12.1
188	>10000	350	9.4
189	3700	94	8
190	>10000	220	10.6
191	>10000	350	4
192	>10000	330	10
193	>10000	390	6
194	10000	165	8

195	10000	100	14.5
196	>10000	240	25
197	7000	145	8
198	>10000	270	14.5
199	>10000	155	1.4
200	>10000	24	17.5
201	>10000	22.4	13.6
202	>10000	54	9.15
203	8500	31	30
204	>10000	25	27.1
205	7300	12.7	2
206	>10000	>10.0	20
207	>10000	30.6	28
208	>10000	27	27
209	>10000	19	20
210	>10000	27	20
211	>10000	33	24
212	>10000	33	20
213	310	<1.0	<1.0
214	1100	<1.0	<1.0
215	250	<1.0	<1.0
216	1000	<1	<1.0
217	600	<1.0	<1.0
218	>10000	<1.0	<1.0
219	>10000	<1.0	<1.0
220	145	<1.0	<1.0
221	1600	<1.0	<1.0
222	100	<1.0	<1.0
223	1100	<1.0	<1.0
224	>10000	18.1	16.7
225	>10000	54	70
226	>10000	18.6	6

227	>10000	<1	<1
228	600	<1.0	<1.0
229	>10000	<1	<1
230	>10000	>100	>100
231	650	<1.0	<1.0
232	<100	<1.0	<1.0

Example 445: *In Vivo Angiogenesis Assay*

The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See, A Model of Angiogenesis in the Mouse Cornea*; Kenyon,BM, et al., Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8.

In this assay, uniformLy sized Hydron™ pellets containing bFGF and sucralfate were prepared and surgically implanted into the stroma mouse cornea adjacent to the temporal limbus. The pellets were formed by making a suspension of 20 µL sterile saline containing 10 µg recombinant bFGF, 10 mg of sucralfate and 10 µL of 12 percent Hydron™ in ethanol. The slurry was then deposited on a 10 x 10 mm piece of sterile nylon mesh. After drying, the nylon fibers of the mesh were separated to release the pellets.

The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy

of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet was placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet was then advanced to the temporal end of the pocket. Antibiotic ointment was then applied to the eye.

Mice were dosed on a daily basis for the duration of the assay. Dosing of the animals was based on bioavailability and overall potency of the compound. an exemplary dose was 10 or 50 mg/kg (mpk) bid, po. Neovascularization of the corneal stroma begins at about day three and was permitted to continue under the influence of the assayed compound until day five. At day five, the degree of angiogenic inhibition was scored by viewing the neovascular progression with a slit lamp microscope.

The mice were anesthetized and the studied eye was once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet was measured. In addition, the contiguous circumferential zone of neovascularization was measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis was calculated as follows.

$$area = \frac{(0.4 \times clock\ hours \times 3.14 \times vessel\ length\ (in\ mm))}{2}$$

Five to six mice were utilized for each compound in each study. The studied mice were thereafter compared to control mice and the difference in the area of neovascularization was recorded as an averaged value. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

Data for four compounds of the above examples are provided below at dosages of 10 and 50 mpk.

Inhibition of Angiogenesis

	Dosage	
Example	10 mpk	50 mpk
Marimastat	--	48 (n=6)
4	18 (n=3)	41 (n=6)
9	50 (n=2)	46 (n=3)
10	47 (n=1)	54 (n=2)
24	53 (n=1)	78 (n=1)

Example 446: *In Vivo* PC-3 Tumor Reduction

PC-3 human pancreatic cancer eclls (ATCC CRL 1435) were grown to 90% confluence in F12/MEM

(Gibco) containing 7% FBS (Gibco). Cells were mechanically harvested using a rubber scraper, and then washed twice with cold medium. The resulting cells were resuspended in cold medium with 30% matrigel (Collaborative Research) and the cell-containing medium was maintained on ice until used.

Balb/c nu/nu mice at 7-9 weeks of age were anesthetized with avertin [2,2,2-tribromethanol/t-amyl alcohol (1 g/1 mL) diluted 1:60 into phosphate-buffered sline] and 3-5x10^6 of the above cells in 0.2 mL of medium were injected into the left flank of each mouse. Cells were injected in the morning, whereas dosing with an inhibitor began at 6 PM. The animals were gavaged BID from day zero (cell injection day) to day 25-30, at which time the animals were euthanized and tumors weighed.

Compounds were dosed at 10 mg/mL in 0.5% methylcellulose/0.1% polysorbate 80 to provide a 50 mg/kg (mpk) dose twice each day, or diluted to provide a 10 mg/kg (mpk) dose twice each day. Tumor measurements began on day 7 and continued every third or fourth day until completion of the study. Groups of ten mice were used in each study and nine to ten survived. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. The results of this study for several of the before discussed compounds are shown below as average reductions in tumor weight.

Average Percentage Reduction

In Tumor Weight

	Dosage	
Example	10 mpk	50 mpk
Marimastat	<5	39 (n=2)
4	33 (n=2)	43 (n=2)
9	40 (n=1)	60 (n=1)
10	nt	59 (n=1)

Example 447: Tumor Necrosis Factor Assays

Cell Culture.

The cells used in the assay are the human moncytic line U-937 (ATCC CRL-1593). The cells are grown in RPMI w/10% FCS and PSG supplement (R-10) and are not permitted to overgrow. The assay is carried out as follows:

1. Count, then harvest cells by centrifugation. Resuspend the pellet in R-10 supplement to a concentration of 1.540 x 10^6 cells/mL.

2. Add test compound in 65 uL R-10 to the appropriate wells of a 96-well flat bottom tissue culture plate. The initial dilution from a DMSO stock (100 mM compound) provides a 400 uM solution, from which five additional three-fold serial dilutions are made. Each dilution of 65 ul (in triplicate) yields final compound test concentrations of 100 μM, 33.3 μM, 11.1 μM, 3.7 μM, 1.2 μM and 0.4 μM.

3. The counted, washed and resuspended cells (200,000 cells/well) in 130 µL are added to the wells.

4. Incubation is for 45 minutes to one hour at 37°C in 5% CO2 in a water saturated container.

5. R-10 (65 uL)containing 160 ng/mL PMA (Sigma) is added to each well.

6. The test system is incubated at 37°C in 5% CO2 overnight (18-20 hours) under 100% humidity.

7. Supernatant, 150 µL, is carefully removed from each well for use in the ELISA assay.

8. For toxicity, a 50 µL aliquot of working solution containg 5 mL R-10, 5 mL MTS solution [CellTiter 96 AQueous One Solution Cell Proliferation Assay Cat.#G358/0,1 (Promega Biotech)] and 250 ul PMS solution are added to each well containing the remaining supernatant and cells and the cells incubated at 37°C in 5% CO_2 until the color develops. The system is excited at 570 nm and read at 630 nm.

TNF Receptor II ELISA Assay

1. Plate 100 µL/well 2 ug/mL mouse anti-human TNFrII antibody (R&D Systems #MAB226) in 1 x PBS (pH 7.1, Gibco) on NUNC-Immuno Maxisorb plate. Incubate the plate at 4°C overnight (about 18-20 hours).

2. Wash the plate with PBS-Tween (1 x PBS w/ 0.05% Tween).

3. Add 200 µL 5% BSA in PBS and block at 37°C in a water saturated atmosphere for 2 hours.

4. Wash the plate with PBS-Tween.

5. Add sample and controls (100 ul of each) to each well. The standards are 0, 50, 100, 200, 300 and 500 pg recombinant human TNFrII (R&D Systems #226-B2) in 100 µL 0.5% BSA in PBS. The assay is linear to between 400-500 pg of standard.

6. Incubate at 37°C in a saturated atmosphere for 1.5 hours.

7. Wash the plate with PBS-Tween.

8. Add 100 µL goat anti-human TNFrII polyclonal (1.5 µg/mL R&D Systems #AB226-PB in 0.5% BSA in PBS).

9. Incubate at 37°C in a saturated atmosphere for 1 hour.

10. Wash the plate with PBS-Tween.

11. Add 100 µL anti-goat IgG-peroxidase (1:50,000 in 0.5% BSA in PBS, Sigma #A5420).

11. Incubate at 37°C in a saturated atmosphere for 1 hour.

12. Wash the plate with PBS-Tween.

13. Add 10 µL KPL TMB developer, develop at room temperature (usually about 10 minutes), then terminate with phosphoric acid and excite at 450 nm and read at 570 nm.

TNFα ELISA Assay

Coat Immulon® 2 plates with 0.1 mL/well of 1ug/mL Genzyme mAb in 0.1 M NaHCO3 pH 8.0 buffer overnight (about 18-20 hours) at 4°C, wrapped tightly in Saran® wrap.

Flick out coating solution and block plates with 0.3 mL/well blocking buffer overnight at 4°C, wrapped in Saran® wrap.

Wash wells thoroughly 4X with wash buffer and completely remove all wash buffer. Add 0.1 mL/well of either samples or rhTNFα standards. Dilute samples if necessary in appropriate diluant (e.g. tissue culture medium). Dilute standard in same diluant. Standards and samples should be in triplicates.

Incubate at 37°C for 1 hour in humified container.

Wash plates as above. Add 0.1 mL/well of 1:200 dilution of Genzyme rabbit anti-hTNF .

Repeat incubation.

Repeat wash. Add 0.1 mL/well of 1 μg/mL Jackson goat anti-rabbit IgG (H+L)-peroxidase.

Incubate at 37°C for 30 minutes.

Repeat wash. Add 0.1 mL/well of peroxide-ABTS solution.

Incubate at room temperature for 5-20 minutes.

Read OD at 405 nm.

12 Reagents are:

Genzyme mouse anti-human TNF? monoclonal (Cat.# 80-3399-01)

Genzyme rabbit anti-human TNF? polyclonal (Cat.#IP-300)

Genzyme recombinant human TNF? (Cat.#TNF-H).

Jackson Immunoresearch peroxide-conjugated goat anti-rabbit IgG (H+L) (Cat.#111-035-144).

Kirkegaard/Perry peroxide ABTS solution (Cat#50-66-01).

Immulon 2 96-well microtiter plates.

Blocking solution is 1 mg/mL gelatin in PBS with 1X thimerasol.

Wash buffer is 0.5 mL Tween® 20 in 1 liter ofPBS.

Results:

Example Number	MTS Toxicity TD_{50} in micromolar	TNFRII Release IC_{50} in micromolar	TNFα Release IC_{50} in micromolar
DMSO	>100	>100	>100
4	>100	>100	>50
6	>100	>100	>50
9	>100	>100	>50
10	>100	>100	>50
13	>100	>100	>50
27	100	>100	>80
35	>100	>100	>80
69	100	>100	>80
95	>100	>100	>50
379	80	>100	80

Example 448: Pharmacokinetic (PK)-evaluation of MMP inhibitors in rats

Under metofane anesthesia, the femoral artery (all 8 rats) and femoral vein (only 4 of 8 rats) are isolated and canulated with PE50 tubing and secured with 3.0 silk suture. The following determinations require two catheters, with the venous line being used for infusion of compound (in the group of rats that receives compound via the intraveneous (IV)route.), and the arterial line being used for collection of blood samples. The rats are

then placed in restraining cages that permit minimal movement and allowed to recover from anesthesia for approximately 30 minutes. At time 0 (prior to dosing), blood samples (400 μL) are collected from arterial cannula.

One group of rats (4 rats per group) receives compound via the oral route at a dosing volume of 2 mL/kg (10mg/mL, dissolved in 0.5% methylcellulose, 0.1% Tween® 20), while the other group of rats receives compound via the intravenous cannula, at a dosing volume of 2 ml/kg (10 mg/mL, dissolved in 10% EtOH, 50% PEG 400, 40% saline). The blood samples are collected from the arterial cannula at 15, 30, 60, 120, 240, and 360 minutes from the oral group with an additional 3 minute sample being collected from IV group. After each sample, the cannulas are flushed with PBS containing 10 units/ml heparin. The animals are subjected to euthanasia with an excess of anesthesia.or carbon monoxide asphyxiation when the study is terminated at 6 hours. Blood samples from each time point are assayed for MMP-13 enzyme inhibitory activity and the circulating concentration of compound plus active metabolites is estimated based on the standard curve.
Pharmacokinetic (PK) parameters are calculated by the VAX computer program CSTRIP. The parameters are defined in textbooks such as *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, eighth ed., McGraw-Hill, Inc., New York (1993) and the references therein.

Example Number	Rat Intraveneous 20 mpk			Rat Oral 20 mpk			
	$t_{1/2}$	AUC (0-∞)	Blood Level @ 3 min	Cmax	AUC (0-6 hr)	BA	Blood Level @ 6 hr
	Hour	hr*μg/mL	μg/mL	μg/mL	hr*μg/mL	%	μg/mL
4	1.77	24.80	37.60	1.84	4.14	16.7	0.254
6	1.19	46.39	84.72	22.88	16.45	35.5	0.345
9	1.10	33.67	42.17	13.63	9.43	28.0	0.281
10	0.84	43.01	73.00	18.47	12.93	30.1	0.134
12	0.86	22.11	73.54	1.00	2.45	11.1	0.121
13	1.03	43.08	91.07	21.98	18.08	42.0	0.228
14	1.25	12.92	12.10	4.13	7.66	59.3	0.102
15	1.01	49.29	120.83	27.16	18.19	36.9	0.192
17	0.74	37.10	63.44	15.72	13.32	35.9	0.135
22	1.47	14.05	18.06	0.82	1.82	13.0	0.174
23	0.85	25.01	59.92	7.31	5.93	23.7	0.087
24	2.49	37.35	62.52	9.79	15.88	42.5	0.545
25	-	-	-	1.48			0.173
26	0.58	17.51	64.01	0.29	0.83	4.7	0.051
27	1.10	43.32	43.69	10.87	21.24	49.0	0.427
28	-	-	-	10.02	24.28		0.537
32	1.03	38.94	51.48	7.65	13.48	34.6	0.529
33	1.91	29.96	24.13	3.33	8.25	27.5	0.543
34	-	-	-	2.13			0.495
35	-	-	-	12.59	26.97		1.237
36	0.65	5.74	19.66	0.16	0.73	12.7	0.072
40	-	-	-	1.55			0.128
42	-	-	-	0.71			0.036
43	0.82	18.79	61.76	4.17	3.24	17.2	0.040
53	0.97	10.78	31.68	0.37	0.48	4.4	BLD
65	-	-	-	0.99			0.080
68	-	-	-	3.41			0.038
69	1.87	63.78	44.00	8.58	22.89	35.9	1.172
70	-	-	-	3.08			0.131
71	-	-	-	4.00			0.452
72	-	-	-	1.42	2.03		0.062
73	-	-	-	1.89	6.87		0.372
79	1.82	6.11	13.99	0.02	0.07	1.1	0.010
80	-	-	40.83	0.03			0.003
81	0.76	38.21	89.01	5.06	6.40	16.7	0.074
89	-	-	-	1.68			0.196
90	-	-	-	0.08			0.041
91	-	-	-	0.17			0.138
93	1.81	13.48	20.88	0.35	1.55	11.5	0.126
94	1.71	25.13	43.37	0.87	1.34	5.3	0.050
95	1.06	19.74	34.71	1.74	4.86	24.6	0.148
96				0.43			0.076
99	0.68	35.68	99.49	14.25	8.05	22.6	0.071
100	1.50	24.60	26.06	3.12	11.30	45.9	0.506
103	1.10	19.66	31.11	2.55	0.09	19.9	0.092
104	0.66	9.86	29.82	9.89	4.88	49.4	0.008
108	-	-	-	2.96			0.108
109	1.12	7.13	13.91	0.93	0.85	11.9	0.027
110			2.67	0.02			0.015

111	0.65	8.49	33.56	0.45	1.11	13.1	0.054
115	1.36	7.81	12.95	1.17	2.00	25.6	0.058
117	0.78	8.69	40.50	0.18	0.28	3.3	0.016
118	1.85	10.97	17.18	0.75	3.32	30.3	0.268
121	-	-	-	0.31			0.055
123	-	-	-	1.43			0.017
125	0.73	15.73	25.36	1.11	2.50	15.9	0.119
233	0.85	23.12	31.90	3.33	6.22	26.9	0.584
379	1.74	51.41	37.54	4.30	16.80	32.7	1.154
382	1.71	73.68	48.81	7.27	36.12	49.0	3.113
387	-	-	-	0.65			0.558
388	0.94	26.10	34.62	0.15	0.68	2.6	0.073
390	1.50	127.63	120.60	23.21	44.20	34.6	1.780
391	1.45	120.92	82.87	24.02	73.24	60.6	2.680
400			104.34	8.55			0.160
408	3.30	25.18	57.40	9.46	4.17	16.6	0.015
410	1.78	29.83	40.08	0.63	2.08	6.7	0.223
414	0.73	26.15	61.89	5.31	6.22	23.8	0.021
416	2.94	230.70	111.17	29.63	156.71	67.9	20.52
418	2.42	209.92	78.55	20.65	77.52	36.9	7.347
421	-	-	-	13.08	19.21		0.206
427	2.85	36.72	50.74	4.16	8.44	23.0	0.440
437	-	-	-	4.21	4.43		0.128
438	2.14	9.05	7.46	0.39	1.86	20.6	0.316

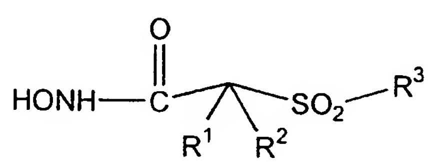
Example Number	Rat Intraveneous 20 mpk			Rat Oral 20 mpk			
	t1/2	AUC (0-∞)	Blood Level @ 3 min	Cmax	AUC (0-6hr)	BA	Blood Level @ 6 hr
	Hour	hr*μg/mL	μg/mL	μg/mL	hr*μg/mL	%	μg/mL
4	1.77	24.80	37.60	1.84	4.14	16.7	0.254
6	1.19	46.39	84.72	22.88	16.45	35.5	0.345
9	1.10	33.67	42.17	13.63	9.43	28.0	0.281
10	0.84	43.01	73.00	18.47	12.93	30.1	0.134
12	0.86	22.11	73.54	1.00	2.45	11.1	0.121
13	1.03	43.08	91.07	21.98	18.08	42.0	0.228
14	1.25	12.92	12.10	4.13	7.66	59.3	0.102
15	1.01	49.29	120.83	27.16	18.19	36.9	0.192
17	0.74	37.10	63.44	15.72	13.32	35.9	0.135
22	1.47	14.05	18.06	0.82	1.82	13.0	0.174
23	0.85	25.01	59.92	7.31	5.93	23.7	0.087
24	2.49	37.35	62.52	9.79	15.88	42.5	0.545
25	-	-	-	1.48			0.173
26	0.58	17.51	64.01	0.29	0.83	4.7	0.051
27	1.10	43.32	43.69	10.87	21.24	49.0	0.427
28	-	-	-	10.02	24.28		0.537
32	1.03	38.94	51.48	7.65	13.48	34.6	0.529
33	1.91	29.96	24.13	3.33	8.25	27.5	0.543
34	-	-	-	2.13			0.495
35	-	-	-	12.59	26.97		1.237
36	0.65	5.74	19.66	0.16	0.73	12.7	0.072
40	-	-	-	1.55			0.128
42	-	-	-	0.71			0.036
43	0.82	18.79	61.76	4.17	3.24	17.2	0.040
53	0.97	10.78	31.68	0.37	0.48	4.4	BLD
65	-	-	-	0.99			0.080
68	-	-	-	3.41			0.038
69	1.87	63.78	44.00	8.58	22.89	35.9	1.172
70	-	-	-	3.08			0.131
71	-	-	-	4.00			0.452
72	-	-	-	1.42	2.03		0.062
73	-	-	-	1.89	6.87		0.372
79	1.82	6.11	13.99	0.02	0.07	1.1	0.010
80	-	-	40.83	0.03			0.003
81	0.76	38.21	89.01	5.06	6.40	16.7	0.074
89	-	-	-	1.68			0.196
90	-	-	-	0.08			0.041
91	-	-	-	0.17			0.138
93	1.81	13.48	20.88	0.35	1.55	11.5	0.126
94	1.71	25.13	43.37	0.87	1.34	5.3	0.050
95	1.06	19.74	34.71	1.74	4.86	24.6	0.148
96				0.43			0.076
99	0.68	35.68	99.49	14.25	8.05	22.6	0.071
100	1.50	24.60	26.06	3.12	11.30	45.9	0.506
103	1.10	19.66	31.11	2.55	0.09	19.9	0.092
104	0.66	9.86	29.82	9.89	4.88	49.4	0.008
108	-	-	-	2.96			0.108
109	1.12	7.13	13.91	0.93	0.85	11.9	0.027
110			2.67	0.02			0.015

111	0.65	8.49	33.56	0.45	1.11	13.1	0.054
115	1.36	7.81	12.95	1.17	2.00	25.6	0.058
117	0.78	8.69	40.50	0.18	0.28	3.3	0.016
118	1.85	10.97	17.18	0.75	3.32	30.3	0.268
121	-	-	-	0.31			0.055
123	-	-	-	1.43			0.017
125	0.73	15.73	25.36	1.11	2.50	15.9	0.119
233	0.85	23.12	31.90	3.33	6.22	26.9	0.584
379	1.74	51.41	37.54	4.30	16.80	32.7	1.154
382	1.71	73.68	48.81	7.27	36.12	49.0	3.113
387	-	-	-	0.65			0.558
388	0.94	26.10	34.62	0.15	0.68	2.6	0.073
390	1.50	127.63	120.60	23.21	44.20	34.6	1.780
391	1.45	120.92	82.87	24.02	73.24	60.6	2.680
400			104.34	8.55			0.160
408	3.30	25.18	57.40	9.46	4.17	16.6	0.015
410	1.78	29.83	40.08	0.63	2.08	6.7	0.223
414	0.73	26.15	61.89	5.31	6.22	23.8	0.021
416	2.94	230.70	111.17	29.63	156.71	67.9	20.52
418	2.42	209.92	78.55	20.65	77.52	36.9	7.347
421	-	-	-	13.08	19.21		0.206
427	2.85	36.72	50.74	4.16	8.44	23.0	0.440
437	-	-	-	4.21	4.43		0.128
438	2.14	9.05	7.46	0.39	1.86	20.6	0.316

From the foregoing, it will be observed that numerous modifications and variations can be effectuated without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation with respect to the specific example presented is intended or should be inferred. The disclosure is intended to cover by the appended claims all such modifications as fall within the scope of the claims.

WHAT IS CLAIMED:

1. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula (I), below



I

wherein

R^1 and R^2 are both hydrido or R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms in the ring that are oxygen, sulfur or nitrogen;

R^3 is an optionally substituted aryl or optionally substituted heteroaryl radical, and when said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl,

arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl, aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl, alkylthioaralkyl, aralkylthioalkyl, an aralkylthioaryl radical, the sulfoxide or sulfone of any of the thio substituents, and a fused ring structure comprising two or more 5- or 6-membered rings selected from the group consisting of aryl, heteroaryl, cycloalkyl and heterocycloalkyl, and (b) is itself optionally substituted with one or more substituents independently selected from the group consisting of a cyano, perfluoroalkyl, trifluoromethoxy, trifluoromethylthio, haloalkyl, trifluoromethylalkyl, aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo, alkyl, alkoxy, nitro, thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino, heteroaryloxy, heteroarylthio, heteroaralkyl, cycloalkyl, heterocyclooxy, heterocyclothio, heterocycloamino, cycloalkyloxy, cycloalkylthio, heteroaralkoxy, heteroaralkylthio, aralkoxy, aralkylthio, aralkylamino, heterocyclo, heteroaryl, arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy, alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy, aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy, alkylthio, alkoxyalkylthio, alkoxycarbonyl, aryloxyalkoxyaryl, arylthioalkylthioaryl, aryloxyalkylthioaryl, arylthioalkoxyaryl, hydroxycarbonylalkoxy, hydroxycarbonylalkylthio, alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,

wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of an alkyl, aryl, heteroaryl,

aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, arylcarbonyl, aralkanoyl, heteroarylcarbonyl, heteroaralkanoyl and an alkanoyl group, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring containing zero to two additional heteroatoms that are nitrogen, oxygen or sulfur and which ring itself is (a) unsubstituted or (b) substituted with one or two groups independently selected from the group consisting of an aryl, alkyl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, alkanoyl, cycloalkyl, heterocycloalkyl, alkoxycarbonyl, hydroxyalkyl, trifluoromethyl, benzofused heterocycloalkyl, hydroxyalkoxyalkyl, aralkoxycarbonyl, hydroxycarbonyl, aryloxycarbonyl, benzofused heterocycloalkoxy, benzofused cycloalkylcarbonyl, heterocycloalkylcarbonyl, and a cycloalkylcarbonyl group,

carbonylamino

wherein the carbonylamino nitrogen is (i) unsubstituted, or (ii) is the reacted amine of an amino acid, or (iii) substituted with one or two radicals selected from the group consisting of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo,

heteroaryl or benzofused heterocycloalkyl ring that is itself unsubstituted or substituted with one or two radicals independently selected from the group consisting of an alkyl, alkoxycarbonyl, nitro, heterocycloalkyl, hydroxy, hydroxycarbonyl, aryl, aralkyl, heteroaralkyl and an amino group,

wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of alkyl, aryl, and heteroaryl, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring,

and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents independently selected from the group consisting of an alkyl, aryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl group, or (iii) wherein the aminoalkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring.

2. The process according to claim 1 wherein R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms in the ring that are oxygen, sulfur or nitrogen;

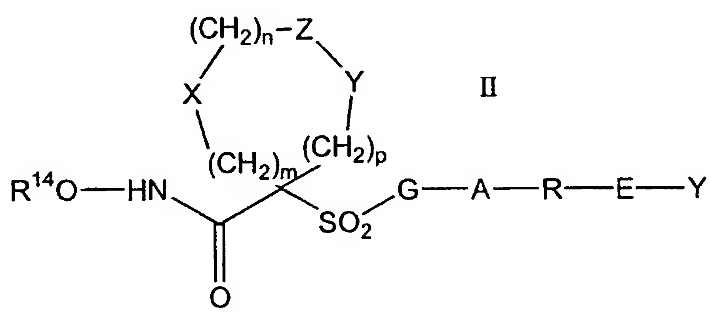
3. The process according to claim 2 wherein R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring or at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C_3-C_{14} alkyl group, a N-piperidyl group, a N-piperazinyl group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group and a benzamido group.

4. The process according to claim 3 wherein R^3 contains two or more 5- or 6-membered rings.

5. The process according to claim 3 wherein R^3, when rotated about an axis drawn through the SO_2-bonded 1-position and the substituent-bonded 4-position of a 6-membered ring or the SO_2-bonded 1-position and substituent-bonded 3- or 4-position of a 5-membered ring, defines a three-dimensional volume whose widest dimension has the width in a direction transverse to that axis to rotation of about one furanyl ring to about two phenyl rings.

6. The process according to claim 3 wherein R^3 has a length that is greater than that of a pentyl group and a length that is less than that of an icosyl group.

7. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula II, below



II

wherein

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of a C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl,

C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

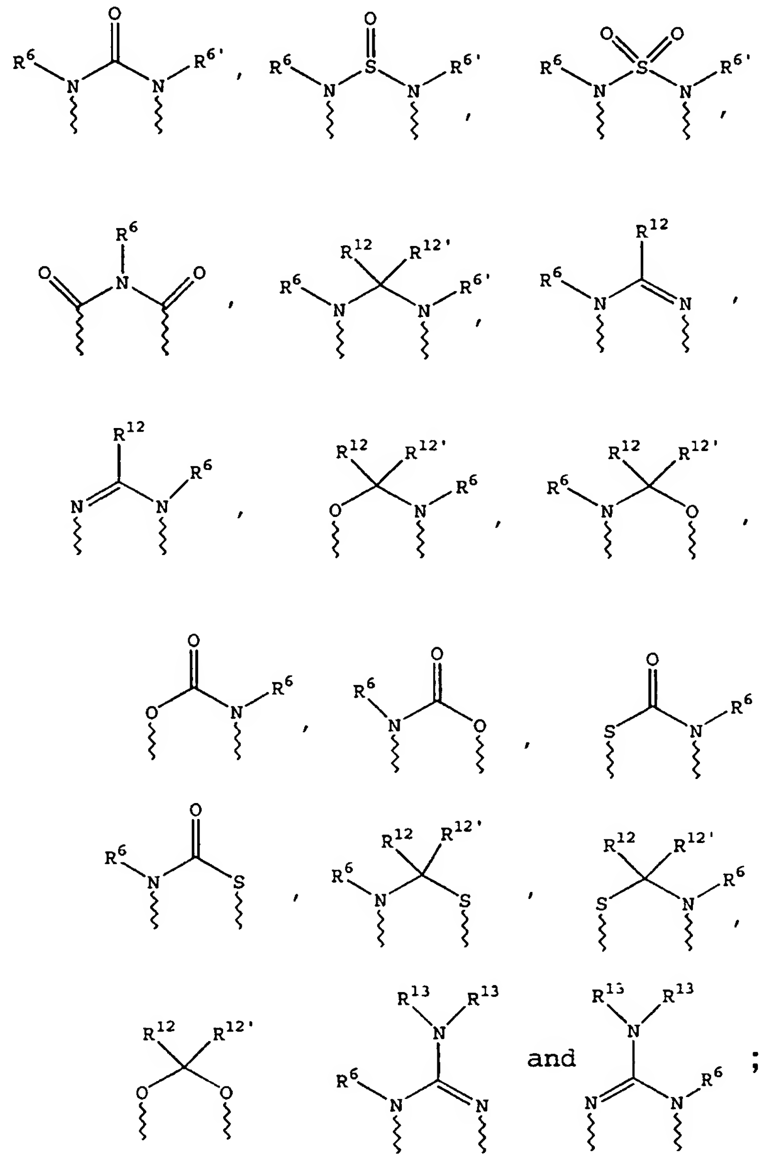
p is zero, 1 or 2;

the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9, and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6 and OC(O), with the remaining one of X, Y and Z being CR^8R^9, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkanoyl, C_6-aryl-C_1-C_6-alkyl, aroyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-

perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, C_6-aryl, C_5-C_6-heterocyclo, C_5-C_6-heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_6-aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, C_6-arylsulfonyl, C_1-C_6-alkylsulfonyl, C_5-C_6-heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, C_6-aryliminocarbonyl, C_5-C_6-heterocycloiminocarbonyl, C_6-arylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, C_6-arylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, C_5-C_6-heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkanoyl, hydroxy-C_1-C_6-alkanoyl, thiol-C_1-C_6-alkanoyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a

C_1-C_6-alkanoyl group, an amino-C_1-C_6-alkylsulfonyl group wherein the amino-C_1-C_6-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group;

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently selected from the group consisting of a hydrido, hydroxy, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroar-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aralkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or

sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl, or wherein R^8 and R^9 or R^{10} and R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11}, or R^8 and R^{10} together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R^8 and R^9 or R^{10} and R^{11} is hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroaralkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-

alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl;

R^{13} is selected from the group consisting of a hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl and a C_1-C_6-hydroxyalkyl group; and

G-A-R-E-Y is a substituent that has a length greater than that of a pentyl group has a length that is less than that of an icosyl group wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^{17}-$;

(4) $-CO-N(R^{17})$ or $-N(R^{17})-CO-$, wherein R^{17} is hydrogen, C_1-C_4-alkyl, or phenyl;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-; and

(13) -CS-N(R^{18})- or -N(R^{18})-CS-, wherein R^{18} is hydrogen C_1-C_4-alkyl, or phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R^{19})- or -(R^{19})CO-, wherein R^{19} is a heterocycloalkyl, or a cycloalkyl group;

(2) -CONH- or -HNCO-; and

(3) -CO-;

(4) $-SO_2-R^{19}-$ or $-R^{19}-SO_2-$;

(5) $-SO_2-$;

(6) $-NH-SO_2-$ or $-SO_2-NH-$; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

8. The process according to claim 7 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

9. The process according to claim 8 wherein each of the two to four rings is 6-membered.

10. The process according to claim 7 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

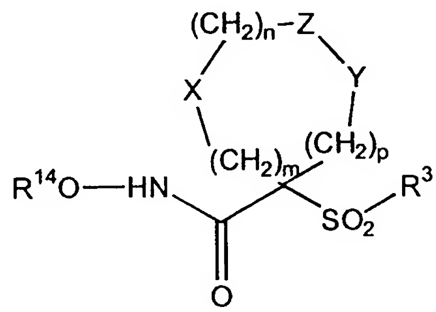
11. The process according to claim 7 wherein A is -O- or -S-.

12. The process according to claim 7 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

13. The process according to claim 7 wherein E is absent.

14. The process according to claim 7 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

15. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula III, below



III

wherein

R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chloro-phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoro-methoxyphenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)phenoxy, 4-(trifluoromethyl-thio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, and a 4-benzyloxyphenoxy group;

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of a C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

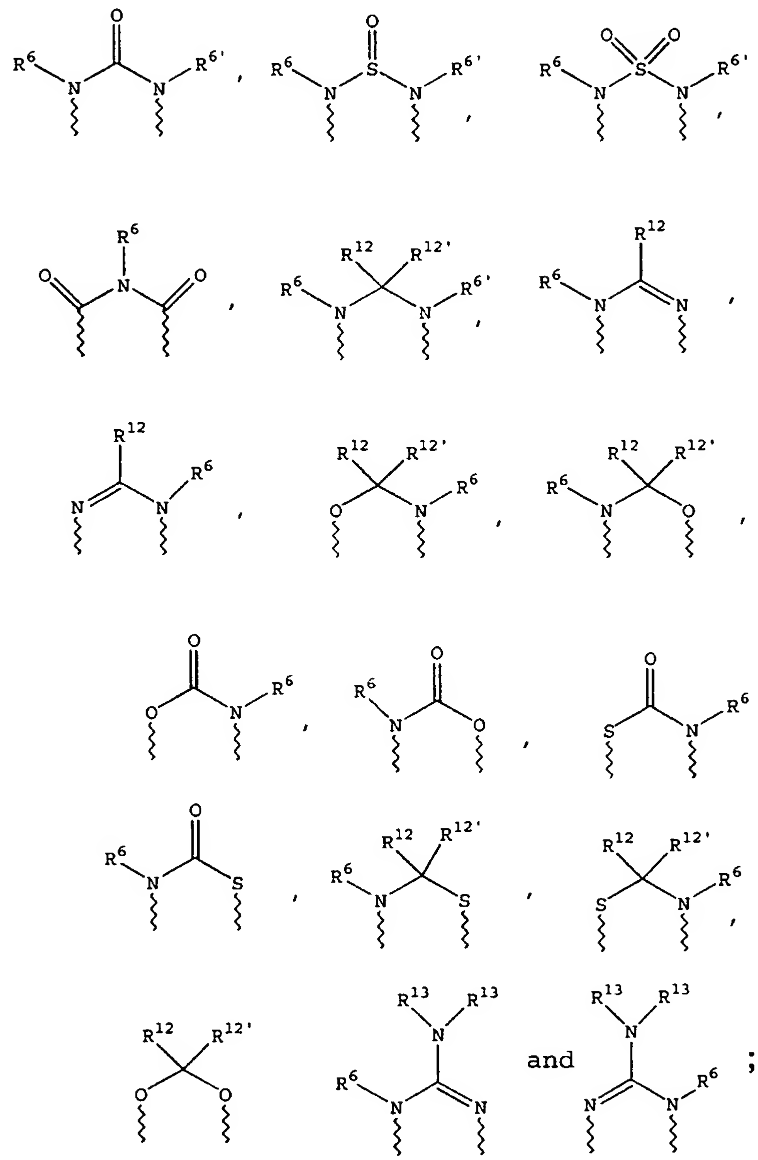
p is zero, 1 or 2;

the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9, and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6 and OC(O), with the remaining one of X, Y and Z being CR^8R^9, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkanoyl, C_6-aryl-C_1-C_6-alkyl, aroyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, C_6-aryl, C_5-C_6-heterocyclo, C_5-C_6-heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_6-aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, C_6-arylsulfonyl, C_1-C_6-alkylsulfonyl, C_5-C_6-heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, C_6-aryliminocarbonyl, C_5-C_6-heterocycloiminocarbonyl, C_6-arylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, C_6-arylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, C_5-C_6-heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkanoyl, hydroxy-C_1-C_6-alkanoyl, thiol-C_1-C_6-alkanoyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group,

hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, an amino-C_1-C_6-alkylsulfonyl group wherein the amino-C_1-C_6-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group;

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently selected from the group consisting of a hydrido, hydroxy, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroar-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aralkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl,

hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl, or wherein R^8 and R^9 or R^{10} and R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11}, or R^8 and R^{10} together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R^8 and R^9 or R^{10} and R^{11} is hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroaralkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-

C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl; and

R^{13} is selected from the group consisting of a hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl and a C_1-C_6-hydroxyalkyl group.

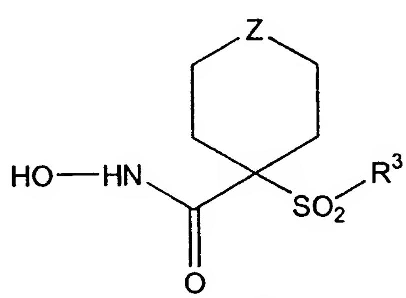
16. The process according to claim 15 wherein the sum of m + n + p = 1 or 2.

17. The process according to claim 15 wherein Z is O, S or NR^6.

18. The process according to claim 15 wherein R^6 is selected from the group consisting of C_3-C_6-cycloalkyl, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, aminosulfonyl, heteroaryl-C_1-C_6-alkyl, aryloxycarbonyl, and C_1-C_6-alkoxycarbonyl.

19. The process according to claim 15 wherein m = n = zero, p= 1, and Y is NR^6.

20. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula IV, below



IV

wherein R^3 is an optionally substituted aryl or optionally substituted heteroaryl radical, and when said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl,

aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl, alkylthioaralkyl, aralkylthioalkyl, an aralkylthioaryl radical, the sulfoxide or sulfone of any of the thio substituents, and a fused ring structure comprising two or more 5- or 6-membered rings selected from the group consisting of aryl, heteroaryl, cycloalkyl and heterocycloalkyl, and (b) is itself optionally substituted with one or more substituents independently selected from the group consisting of a cyano, perfluoroalkyl, trifluoromethoxy, trifluoromethylthio, haloalkyl, trifluoromethylalkyl, aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo, alkyl, alkoxy, nitro, thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino, heteroaryloxy, heteroarylthio, heteroaralkyl, cycloalkyl, heterocyclooxy, heterocyclothio, heterocycloamino, cycloalkyloxy, cycloalkylthio, heteroaralkoxy, heteroaralkylthio, aralkoxy, aralkylthio, aralkylamino, heterocyclo, heteroaryl, arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy, alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy, aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy, alkylthio, alkoxyalkylthio, alkoxycarbonyl, aryloxyalkoxyaryl, arylthioalkylthioaryl, aryloxyalkylthioaryl, arylthioalkoxyaryl, hydroxycarbonylalkoxy, hydroxycarbonylalkylthio, alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,

wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of an alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, aralkoxycarbonyl,

alkoxycarbonyl, arylcarbonyl, aralkanoyl, heteroarylcarbonyl, heteroaralkanoyl and an alkanoyl group, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring containing zero to two additional heteroatoms that are nitrogen, oxygen or sulfur and which ring itself is (a) unsubstituted or (b) substituted with one or two groups independently selected from the group consisting of an aryl, alkyl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, alkanoyl, cycloalkyl, heterocycloalkyl, alkoxycarbonyl, hydroxyalkyl, trifluoromethyl, benzofused heterocycloalkyl, hydroxyalkoxyalkyl, aralkoxycarbonyl, hydroxycarbonyl, aryloxycarbonyl, benzofused heterocycloalkoxy, benzofused cycloalkylcarbonyl, heterocyclo-alkylcarbonyl, and a cycloalkylcarbonyl group,

carbonylamino

wherein the carbonylamino nitrogen is (i) unsubstituted, or (ii) is the reacted amine of an amino acid, or (iii) substituted with one or two radicals selected from the group consisting of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo, heteroaryl or benzofused heterocycloalkyl ring

that is itself unsubstituted or substituted with one or two radicals independently selected from the group consisting of an alkyl, alkoxycarbonyl, nitro, heterocycloalkyl, hydroxy, hydroxycarbonyl, aryl, aralkyl, heteroaralkyl and an amino group,

wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of alkyl, aryl, and heteroaryl, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring,

and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents independently selected from the group consisting of an alkyl, aryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl group, or (iii) wherein the aminoalkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring; and

Z is selected group the group consisting of O, S, NR^6, SO, SO_2, and NSO_2R^7,

wherein R^6 is selected from the group consisting of hydrido, C_1-C_5-alkyl, C_1-C_5-alkanoyl, benzyl, benzoyl, C_3-C_5-alkynyl, C_3-C_5-alkenyl, C_1-C_3-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl, heteroaryl-C_1-C_6-alkyl, C_1-C_5-hydroxyalkyl, C_1-C_5-carboxyalkyl, C_1-

C_5-alkoxy C_1-C_5-alkylcarbonyl, and NR^8R^9-C_1-C_5-alkylcarbonyl or NR^8R^9-C_1-C_5-alkyl wherein R^8 and R^9 are independently hydrido, C_1-C_5-alkyl, C_1-C_5-alkoxycarbonyl or aryl-C_1-C_5-alkoxycarbonyl, or NR^8R^9 together form a heterocyclic ring containing 5- to 8-atoms in the ring; and

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group.

21. The process according to claim 20 wherein R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring or at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C_3-C_{14} alkyl group, a N-piperidyl group, a N-piperazinyl group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group and a benzamido group.

22. The process according to claim 20 wherein R^3 has a length that is greater than that of a pentyl group and a length that is less than that of an icosyl group.

23. The process according to claim 20 wherein Z is O, S or NR^6.

24. The process according to claim 23 wherein R^6 is selected from the group consisting of C_3-C_6-cycloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, amino-C_1-C_6-alkyl, aminosulfonyl, heteroaryl-C_1-C_6-alkyl, aryloxycarbonyl, and C_1-C_6-alkoxycarbonyl.

25. The process according to claim 20 wherein said R^3 radical is the substituent G-A-R-E-Y, wherein G is an aryl or heteroaryl group;

A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^{17}-$;

(4) $-CO-N(R^{17})$ or $-N(R^{17})-CO-$, wherein R^{17} is hydrogen, C_1-C_4-alkyl, or phenyl;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-; and

(13) $-CS-N(R^{18})-$ or $-N(R^{18})-CS-$, wherein R^{18} is hydrogen C_1-C_4-alkyl, or phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R^{19})- or -(R^{19})CO-, wherein R^{19} is a heterocycloalkyl, or a cycloalkyl group;

(2) -CONH- or -HNCO-; and

(3) -CO-;

(4) -SO_2-R^{19}- or -R^{19}-SO_2-;

(5) -SO_2-;

(6) -NH-SO_2- or -SO_2-NH-; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

26. The process according to claim 25 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

27. The process according to claim 26 wherein each of the two to four rings is 6-membered.

28. The process according to claim 25 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

29. The process according to claim 25 wherein A is -O- or -S-.

30. The process according to claim 25 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

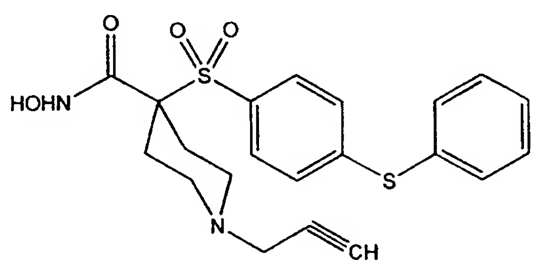
31. The process according to claim 25 wherein E is absent.

32. The process according to claim 25 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

33. The process according to claim 20 wherein R^3 is a radical that is comprised of a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chlorophenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxy-phenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)-phenoxy, 4-(trifluoromethylthio)-thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methylphenoxy, 4-ethoxyphenoxy, 3,4-

difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, N-piperidyl, N-piperazinyl and a 4-benzyloxyphenoxy group.

34. The process according to claim 20 wherein said inhibitor corresponds in structure to the formula



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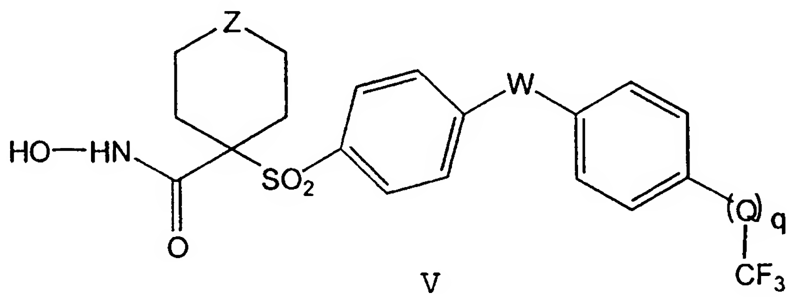
35. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula V, below



V

wherein

Z is O, S or NR^6;

W and Q are independently oxygen (O), NR^6 or sulfur (S),

R^6 is selected from the group consisting of C_3-C_6-cycloalkyl, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, aminosulfonyl, heteroaryl-C_1-C_6-alkyl, aryloxycarbonyl, and C_1-C_6-alkoxycarbonyl; and

q is zero or one such that when q is zero, Q is absent and the trifluoromethyl group is bonded directly to the depicted phenyl ring.

36. The process according to claim 35 wherein q is zero.

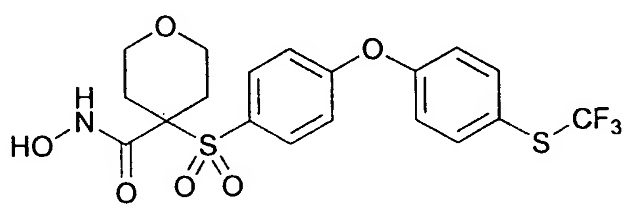
37. The process according to claim 35 wherein W is O.

38. The process according to claim 37 wherein q is zero.

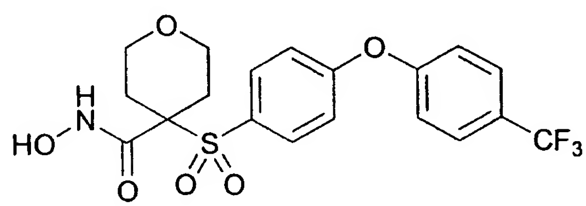
39. The process according to claim 37 wherein q is one and Q is O.

40. The process according to claim 37 wherein q is one and Q is S.

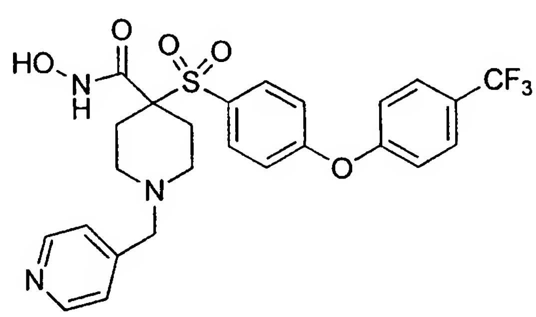
41. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



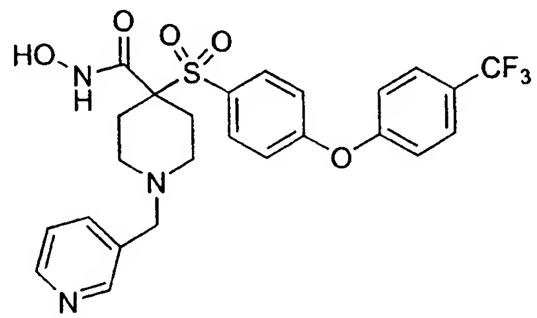
42. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



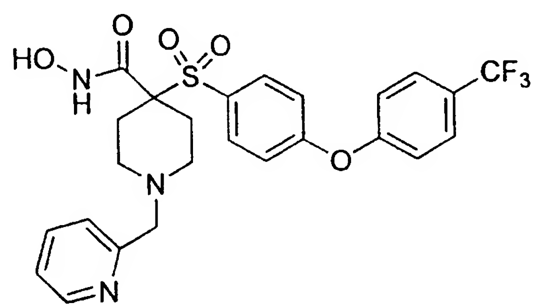
43. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



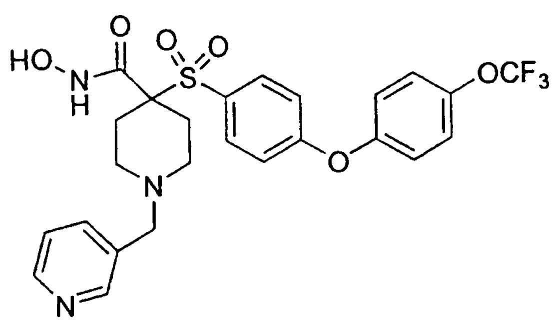
44. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



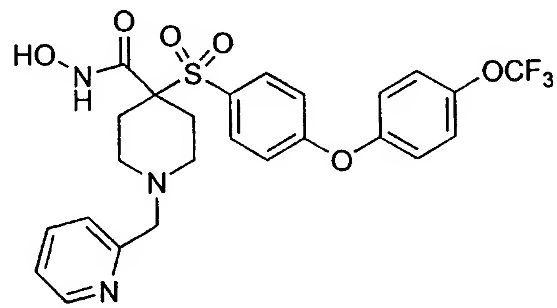
45. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



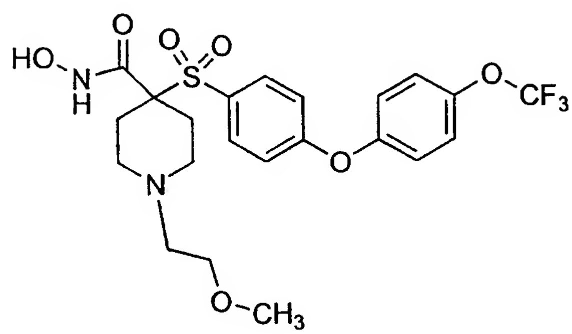
46. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



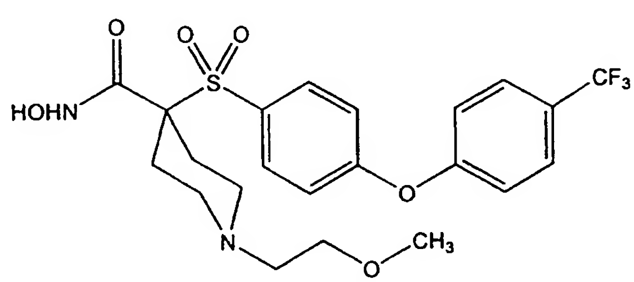
47. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



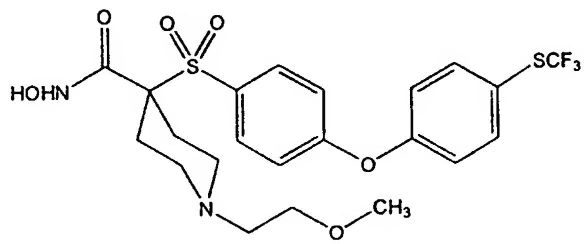
48. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



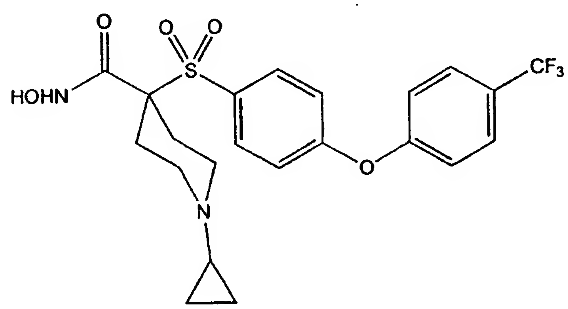
49. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



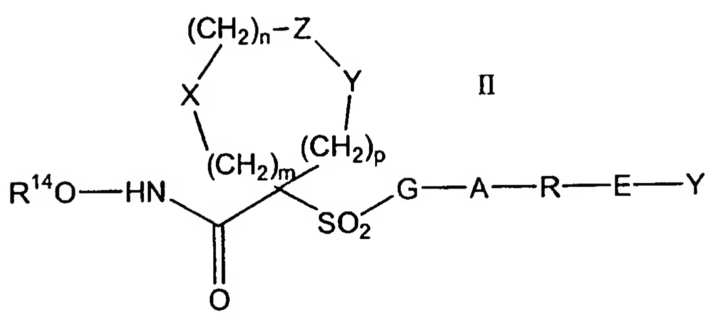
50. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



51. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



52. A compound corresponding in structure to formula II, below, or a pharmaceutically acceptable salt thereof:



II

wherein

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of an C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl,

C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

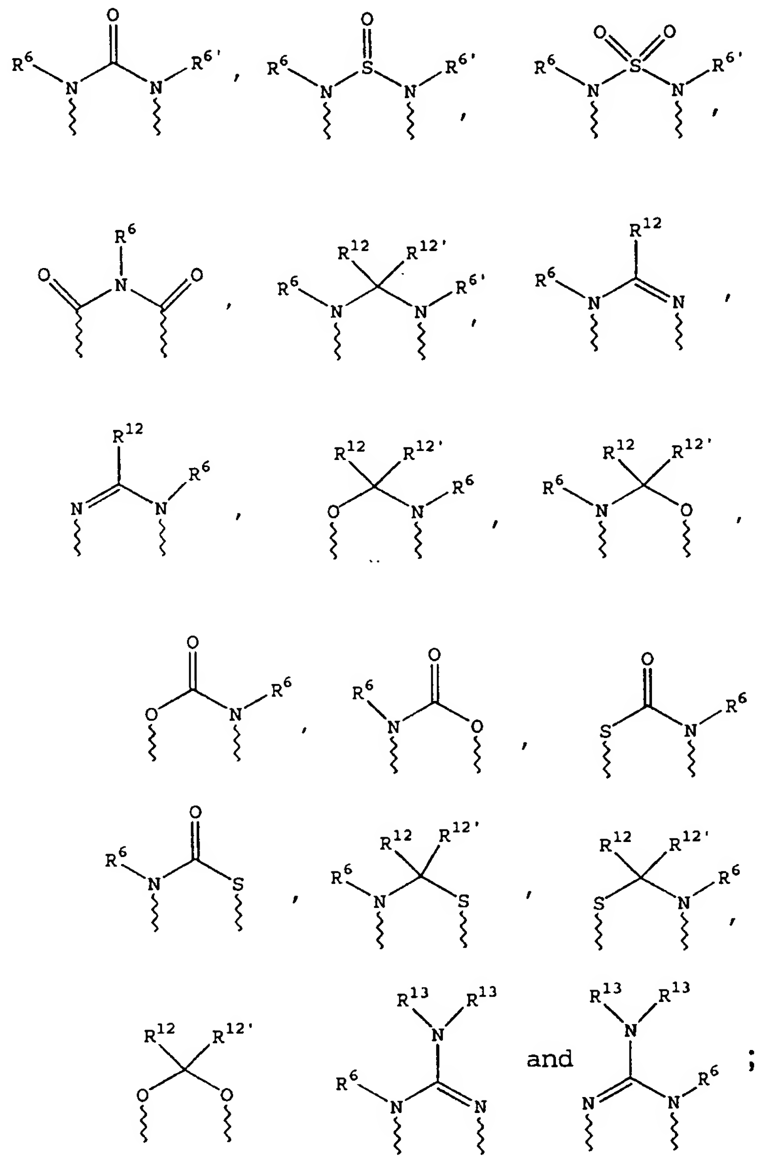
p is zero, 1 or 2;

the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9, and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6 and OC(O), with the remaining one of X, Y and Z being CR^8R^9, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkanoyl, C_6-aryl-C_1-C_6-alkyl, aroyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-

perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, C_6-aryl, C_5-C_6-heterocyclo, C_5-C_6-heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_6-aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, C_6-arylsulfonyl, C_1-C_6-alkylsulfonyl, C_5-C_6-heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, C_6-aryliminocarbonyl, C_5-C_6-heterocycloiminocarbonyl, C_6-arylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, C_6-arylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, C_5-C_6-heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkanoyl, hydroxy-C_1-C_6-alkanoyl, thiol-C_1-C_6-alkanoyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a

C_1-C_6-alkanoyl group, an amino-C_1-C_6-alkylsulfonyl group wherein the amino-C_1-C_6-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group;

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently selected from the group consisting of a hydrido, hydroxy, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroar-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aralkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or

sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl, or wherein R^8 and R^9 or R^{10} and R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11}, or R^8 and R^{10} together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R^8 and R^9 or R^{10} and R^{11} is hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroaralkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-

alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl;

R^{13} is selected from the group consisting of a hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl and a C_1-C_6-hydroxyalkyl group; and

G-A-R-E-Y is a substituent that has a length greater than that of a pentyl group a length that is less than that of an icosyl group, and wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^{17}-$;

(4) $-CO-N(R^{17})$ or $-N(R^{17})-CO-$, wherein R^{17} is hydrogen, C_1-C_4-alkyl, or phenyl;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-; and

(13) $-CS-N(R^{18})-$ or $-N(R^{18})-CS-$, wherein R^{18} is hydrogen C_1-C_4-alkyl, or phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) $-CO(R^{19})-$ or $-(R^{19})CO-$, wherein R^{19} is a heterocycloalkyl, or a cycloalkyl group;

(2) -CONH- or -HNCO-; and

(3) -CO-;

(4) $-SO_2-R^{19}-$ or $-R^{19}-SO_2-$;

(5) $-SO_2-$;

(6) $-NH-SO_2-$ or $-SO_2-NH-$; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

53. The compound according to claim 52 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

54. The compound according to claim 52 wherein each of the two to four rings is 6-membered.

55. The compound according to claim 52 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

56. The compound according to claim 52 wherein A is -O- or -S-.

57. The compound according to claim 52 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

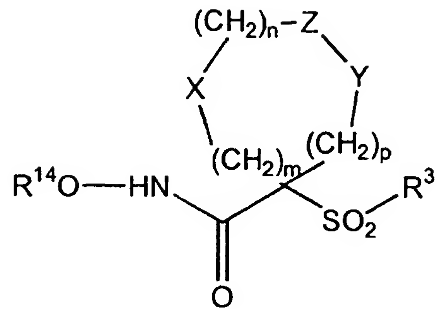
58. The compound according to claim 52 wherein E is absent.

59. The compound according to claim 52 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

60. The compound according to claim 52 wherein R^{14} is hydrido.

61. The compound according to claim 52 wherein W of the $C(W)R^{15}$ is O and R^{15} is a C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, or aryloxy group.

62. A compound corresponding in structure to formula III, below, or a pharmaceutically acceptable salt thereof



III

wherein

R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chloro-phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoro-methoxyphenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)phenoxy, 4-(trifluoromethyl-thio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-

tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, and a 4-benzyloxyphenoxy group;

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of a C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, ar-C_1-C_6-alkoxy, ar-C_1-C_6-alkyl, heteroaryl and amino C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, ar-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkanoyl radical, or (iii) wherein the amino C_1-C_6-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

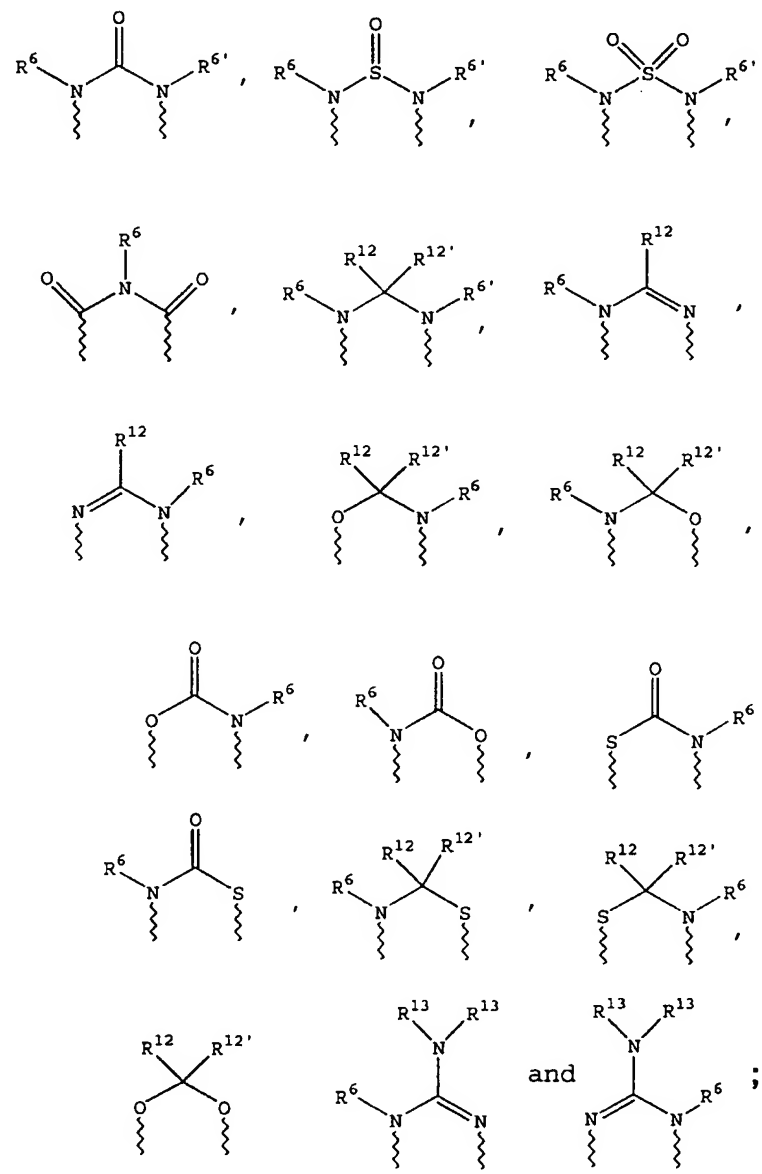
the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9, and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O,

SS, NR^6NR^6 and OC(O), with the remaining one of X, Y and Z being CR^8R^9, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkanoyl, C_6-aryl-C_1-C_6-alkyl, aroyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, C_6-aryl, C_5-C_6-heterocyclo, C_5-C_6-heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_6-aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, C_6-arylsulfonyl, C_1-C_6-alkylsulfonyl, C_5-C_6-heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, C_6-aryliminocarbonyl, C_5-C_6-heterocycloiminocarbonyl, C_6-arylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, C_6-arylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, C_5-C_6-heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkanoyl, hydroxy-C_1-C_6-alkanoyl, thiol-C_1-C_6-alkanoyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group

consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group, an amino-C_1-C_6-alkylsulfonyl group wherein the amino-C_1-C_6-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, C_3-C_8-cycloalkyl and a C_1-C_6-alkanoyl group;

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently selected from the group consisting of a hydrido, hydroxy, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroar-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-

alkyl, aralkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl, or wherein R^8 and R^9 or R^{10} and R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11}, or R^8 and R^{10} together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R^8 and R^9 or R^{10} and R^{11} is hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of a hydrido, C_1-C_6-alkyl, aryl, ar-C_1-C_6-alkyl, heteroaryl, heteroaralkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-

alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylar-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl and an amino-C_1-C_6-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1-C_6-alkyl, ar-C_1-C_6-alkyl, cycloalkyl and C_1-C_6-alkanoyl; and

R^{13} is selected from the group consisting of a hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl and a C_1-C_6-hydroxyalkyl group.

63. The compound according to claim 62 wherein the sum of m + n + p = 1 or 2.

64. The compound according to claim 62 wherein Z is O, S or NR^6.

65. The compound according to claim 62 wherein R^6 is selected from the group consisting of C_3-C_6-cycloalkyl, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl,

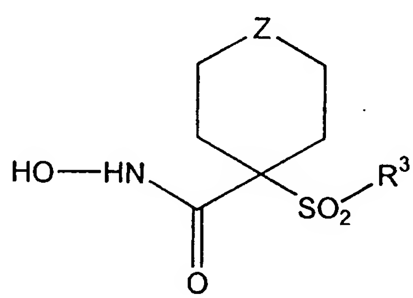
aminosulfonyl, heteroaryl-C_1-C_6-alkyl, aryloxycarbonyl, and C_1-C_6-alkoxycarbonyl.

66. The compound according to claim 62 wherein m = n = zero, p= 1, and Y is NR^6.

67. The compound according to claim 62 wherein R^{14} is hydrido.

68. The compound according to claim 62 wherein W of the $C(W)R^{15}$ is O and R^{15} is a C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, or aryloxy group.

69. A compound corresponding in structure to formula IV, below, or a pharmaceutically acceptable salt thereof



IV

wherein R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring or at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C_3-C_{14} alkyl group, a N-piperidyl group, a N-piperazinyl group, a phenoxy group, a

thiophenoxy group, a 4-thiopyridyl group, a phenylazo group and a benzamido group; and

Z is selected group the group consisting of O, S, NR^6, SO, SO_2, and NSO_2R^7,

wherein R^6 is selected from the group consisting of hydrido, C_1-C_5-alkyl, C_1-C_5-alkanoyl, ' benzyl, benzoyl, C_3-C_5-alkynyl, C_3-C_5-alkenyl, C_1-C_3-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl, heteroaryl-C_1-C_6-alkyl, C_1-C_5-hydroxyalkyl, C_1-C_5-carboxyalkyl, C_1-C_5-alkoxy C_1-C_5-alkylcarbonyl, and NR^8R^9-C_1-C_5-alkylcarbonyl or NR^8R^9-C_1-C_5-alkyl wherein R^8 and R^9 are independently hydrido, C_1-C_5-alkyl, C_1-C_5-alkoxycarbonyl or aryl-C_1-C_5-alkoxycarbonyl, or NR^8R^9 together form a heterocyclic ring containing 5- to 8-atoms in the ring; and

R^7 is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl and a C_1-C_6-hydroxyalkyl group.

70. The compound according to claim 69 wherein R^3 has a length that is greater than that of a pentyl group and a length that is less than that of an icosyl group.

71. The compound according to claim 69 wherein Z is O, S or NR^6.

72. The compound according to claim 69 wherein R^6 is selected from the group consisting of C_3-C_6-cycloalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, amino-C_1-C_6-alkyl, aminosulfonyl, heteroaryl-C_1-C_6-alkyl, aryloxycarbonyl, and C_1-C_6-alkoxycarbonyl.

73. The compound according to claim 69 wherein said R^3 radical is the substituent G-A-R-E-Y, wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

(1) -O-;

(2) -S-;

(3) $-NR^{17}-$;

(4) $-CO-N(R^{17})$ or $-N(R^{17})-CO-$, wherein R^{17} is hydrogen, C_1-C_4-alkyl, or phenyl;

(5) -CO-O- or -O-CO-;

(6) -O-CO-O-;

(7) -HC=CH-;

(8) -NH-CO-NH-;

(9) -C≡C-;

(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-; and

(13) $-CS-N(R^{18})-$ or $-N(R^{18})-CS-$, wherein R^{18} is hydrogen C_1-C_4-alkyl, or phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R^{19})- or -(R^{19})CO-, wherein R^{19} is a heterocycloalkyl, or a cycloalkyl group;

(2) -CONH- or -HNCO-; and

(3) -CO-;

(4) -SO_2-R^{19}- or -R^{19}-SO_2-;

(5) -SO_2-;

(6) -NH-SO_2- or -SO_2-NH-; or

(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

74. The compound according to claim 69 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

75. The compound according to claim 69 wherein each of the two to four rings is 6-membered.

76. The compound according to claim 69 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.